Official Protocol Title:	A Phase 1b Multi-cohort Study of the Combination of Pembrolizumab (MK-3475) plus Binimetinib alone or the Combination of Pembrolizumab plus Chemotherapy with or without Binimetinib in Participants with Metastatic Colorectal Cancer (KEYNOTE-651)
NCT number:	NCT03374254
Document Date:	08-Jun-2022

Title Page

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Protocol Title: A Phase 1b Multi-cohort Study of the Combination of Pembrolizumab (MK-3475) plus Binimetinib alone or the Combination of Pembrolizumab plus Chemotherapy with or without Binimetinib in Participants with Metastatic Colorectal Cancer (KEYNOTE-651)

Protocol Number: 651-04

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND NUMBER: 123482

EudraCT NUMBER: 2017-000356-26

Approval Date: 08 June 2022

Sponsor Signatory

Typed Name:		Date
Title:		

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:		Date
Title:		

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	08-JUN-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 3	19-MAY-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 2	07-MAY-2020	Clarify that DPD testing is not required at Screening but will be based on "known" medical history.
Amendment 1	16-NOV-2017	Provide rationale for the use of chemotherapy (FOLFOX) in combination with pembrolizumab and to provide an assessment of the risk of overlapping toxicities with chemotherapy combinations
Original Protocol	25-JUL-2017	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 04

Overall Rationale for the Amendment:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 12.4 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

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1. Synopsis

Protocol Title:

A Phase 1b Multi-cohort Study of the Combination of Pembrolizumab (MK-3475) plus Binimetinib alone or the Combination of Pembrolizumab plus Chemotherapy with or without Binimetinib in Participants with Metastatic Colorectal Cancer (KEYNOTE-651)

Short Title:

Ph1b study of MK-3475 with chemotherapy and/or binimetinib in participants with mCRC

Objectives/Hypotheses and Endpoints:

The objectives and endpoints apply to all participants enrolled in the trial. There is no intent to compare Cohorts B and C or Cohorts D and E. Each cohort will have independent objectives and will be analyzed separately.

Objective/Hypothesis	Endpoint
Primary	
Objectives: • To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) for the following cohorts: o Cohort A (pembrolizumab in combination with binimetinib in metastatic colorectal cancer (mCRC) participants previously treated with fluoropyrimidine, irinotecan, and oxaliplatin). o Cohort B (pembrolizumab in combination with mFOLFOX7 in previously untreated mCRC participants). o Cohort C (pembrolizumab in combination with mFOLFOX7 and binimetinib in previously untreated mCRC participants).	• Determined by incidence of dose limiting toxicities (DLTs)

○ Cohort D (pembrolizumab in combination with FOLFIRI in mCRC participants previously treated with one line of a fluoropyrimidine plus oxaliplatin-based regimen). ○ Cohort E (pembrolizumab in combination with FOLFIRI and binimetinib in mCRC participants previously treated with one line of fluoropyrimidine plus oxaliplatin-based regimen).	
Secondary	
Objective: • To evaluate the objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as assessed by the investigator for each cohort.	**Endpoint:** • Objective response rate (ORR): defined as the proportion of participants in the analysis population who experience complete response (CR) or partial response (PR) as assessed by the investigator based on RECIST Version 1.1.

Overall Design:

Trial Phase	Phase 1b
Clinical Indication	The treatment of participants with metastatic colorectal cancer (mCRC)
Population	Participants with mCRC with the non-microsatellite instability high/proficient mismatch repair (non-MSI-H/pMMR) phenotype
Trial Type	Interventional
Type of Design	Open label, multicenter, international, cohort-based, dose finding and dose confirmation Phase 1b
Type of Control	No treatment control
Trial Blinding	Unblinded Open-label

Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 48 months from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

A maximum of approximately 220 participants will be enrolled (Parts 1 and 2). A target sample size of 159 participants will be used for trial planning purposes.

Treatment Groups and Duration:

Treatment Groups	This trial includes 2 parts: Part 1 will be a dose finding phase using the modified toxicity probability interval (mTPI) design and Part 2 will be a dose confirmation phase to further examine safety and exploratory efficacy. There are a total of 5 cohorts. Each of the 5 cohorts will participate in Part 1 and Part 2. The study will evaluate safety, tolerability, and efficacy in the following 5 cohorts: **Cohort A:** **Part 1**: Dose Finding Standard dose (DL1): Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W) + binimetinib (oral) 30 mg twice daily (BID) Escalation dose (DL2): Pembrolizumab 200 mg IV Q3W + binimetinib 45 mg (oral) BID **Part 2**: Dose Confirmation Pembrolizumab 200 mg IV Q3W + binimetinib (oral) (preliminary RP2D) BID **Cohort B:** **Part 1**: Dose Finding DL1: Pembrolizumab 200 mg IV Q3W + mFOLFOX7 (oxaliplatin [85 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; fluorouracil [5-FU] 2400 mg/m^2 over 46 to 48 hours) IV every 2 weeks (Q2W). De-escalation dose (DL-1): Pembrolizumab 200 mg IV Q3W + mFOLFOX7 (oxaliplatin [70 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU [2000 mg/m^2 over 46 to 48 hours]) IV Q2W

	Part 2: Dose Confirmation Pembrolizumab 200 mg Q3W + mFOLFOX7 (preliminary RP2D) IV Q2W **Cohort C:** **Part 1**: Dose Finding DL1: Pembrolizumab 200 mg IV Q3W + mFOLFOX7 (preliminary RP2D determined in Cohort B) IV Q2W + binimetinib 30 mg (oral) BID DL2: Pembrolizumab 200 mg IV Q3W + mFOLFOX7 (preliminary RP2D determined in Cohort B) IV Q2W + binimetinib 45 mg (oral) BID **Part 2**: Dose Confirmation Pembrolizumab 200 mg IV Q3W + mFOLFOX7 (preliminary RP2D determined in Cohort B) IV Q2W + binimetinib (preliminary RP2D) (oral) BID **Cohort D:** **Part 1**: Dose Finding DL1: Pembrolizumab 200 mg IV Q3W + FOLFIRI (irinotecan [180 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU [2400 mg/m^2 over 46 to 48 hours]) IV Q2W DL-1: Pembrolizumab 200 mg IV Q3W + FOLFIRI dose may be de-escalated (irinotecan [150 mg/m^2]; leucovorin (calcium folinate) [400 mg/m^2]; 5-FU 2000 mg/m^2 over 46 to 48 hours]) IV Q2W **Part 2**: Dose Confirmation Pembrolizumab 200 mg IV Q3W + FOLFIRI (preliminary RP2D) IV Q2W **Cohort E:** **Part 1**: Dose Finding DL1: Pembrolizumab 200 mg IV Q3W + FOLFIRI (preliminary RP2D determined in Cohort D) IV Q2W + binimetinib 30 mg (oral) BID DL2: Pembrolizumab 200 mg IV Q3W + FOLFIRI (preliminary RP2D determined in Cohort D) IV Q2W + binimetinib 45 mg (oral) BID

	Part 2: Dose Confirmation Pembrolizumab 200 mg IV Q3W + FOLFIRI (preliminary RP2D determined in Cohort D) IV Q2W + binimetinib (preliminary RP2D) (oral) BID
Duration of Participation	Each participant will participate in the trial from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each participant will be assigned to receive study treatment until disease progression is radiographically documented and confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years) and binimetinib treatment. Treatment with standard of care (SOC) chemotherapy (mFOLFOX7 or FOLFIRI) will continue per Investigator's decision. Once the participant has achieved the study objective or study has ended, the participant is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

A list of abbreviations used in this document can be found in Appendix 1. Study governance considerations are outlined in Appendix 4.

2. Schedule of Activities (SoA)

2.1 Pembrolizumab in Combination with Binimetinib (Cohort A)

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment	Post-treatment			Notes
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up	
											At time of discon	30 days post-discon	Q9W post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Administrative Procedures															
Informed Consent	X														
Informed Consent for optional post-treatment tumor biopsy	X														
Informed Consent for FBR (optional)	X														
Participant Identification Card		X													
Inclusion/Exclusion Criteria		X													
Demographics and Medical History		X													
Cancer disease status and Prior Treatment history		X													
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X			
Pembrolizumab Administration			X	X	X	X	X	X	X	X					
Binimetinib Administration			<==========X==========→												To be administered BID.
Efficacy Assessments															
Tumor Imaging		X	<==========X==========→								X		X		Tumor imaging at screening must be performed within 28 days prior to the date of Cycle 1 Day 1. On-study imaging will be performed every 9 weeks (63 days ± 7 days) calculated from the date of allocation. See section 9.2.

Pembrolizumab in Combination with Binimetinib (Cohort A)

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment	Post-treatment			Notes
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up	
											At time of discon	30 days post-discon	Q9W post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Clinical Procedures/ Assessments															
Review Adverse Events		X	<==========X==========→									X	X		
Full Physical Examination		X									X				
Full Ophthalmic Examination (Q8W)	X			X	<==========X==========→						X				To be performed at screening, Cycle 2 Day 1 and then every 8 weeks (±7 days) from Cycle 2 Day 1 and EOT. An ophthalmic examination at the 30-day follow up is only required if there was a clinically significant abnormality noted at EOT (± 7 days)
Directed Physical Examination			X	X	X	X	X	X	X	X					
Height, Weight, and Vital Signs		X	X	X	X	X	X	X	X	X	X				Height will be measured at Visit 1 only.
12-Lead Electrocardiogram		X		X	X	X	X	X	X	X	X	X			ECG will be performed in triplicate to confirm QTc interval at screening. ECG will be performed predose starting at Cycle 2.
Echocardiogram/ MUGA scan (Q12W)	X			X			X			X	X				ECHO/MUGA scans are to be performed at Screening and pre-dose on Cycle 2 Day 1 and Cycle 5 Day 1, then every 12 weeks and EOT.
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X				ECOG Performance Status at Screening to be assessed within 7 days prior to the first dose of trial treatment.

Pembrolizumab in Combination with Binimetinib (Cohort A)

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment	Post-treatment			Notes
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up	
											At time of discon	30 days post-discon	Q9W post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	± 3	±3	±3	±3	±3	±3	±7	±14	
Post-study Anticancer Therapy Status													X	X	
Survival Status			<==========X==========→											X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
LOCAL Laboratory Assessments															
MSI/MMR Status	X														If tumor testing is obtained by both PCR and IHC, the tumor result should be neither MSI-H by PCR nor dMMR by IHC to identify the non-MSI-H participants.
Pregnancy Test – Urine or Serum β-hCG, if applicable		X	X												Pregnancy tests may be performed if clinically warranted, or as defined by local regulations.
PT/INR and aPTT		X													
CBC with Differential[a]		X	X	X	X	X	X	X	X	X	X	X			
Chemistry Panel[a]		X	X	X	X	X	X	X	X	X	X	X			
Urinalysis[a]		X		X		X		X		X	X	X			To be performed at screening, and every other cycle starting at Cycle 2.
T3 or FT3, FT4, TSH		X		X		X		X		X	X	X			To be performed at screening, and every other cycle starting at Cycle 2.
Serum Tumor Marker			<==========X==========→								X	X			Serum tumor marker (CEA) to be collected Q3W starting at Cycle 1.
CENTRAL Laboratory Assessments															
Binimetinib Pharmacokinetics			X												PK samples will be collected at time 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6 hrs (all ±10 min) on Day 15, pre-dose (24 ± 2 hrs from the first binimetinib PK collection) on Day 16 and pre-dose (48 ± 2 hrs from the first binimetinib PK collection) on Day 17 in Cycle 1. The exact time of sample collection and time of administration of binimetinib will be recorded.
Blood for Genetic Analysis			X												To be collected pre-dose.

Pembrolizumab in Combination with Binimetinib (Cohort A)

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)								End of Treatment	Post-treatment			Notes
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up	
											At time of discon	30 days post-discon	Q9W post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±14	
Blood for RNA Analyses			X	X			X				X				Samples should be obtained pre-dose of Cycle 1, Cycle 2, and Cycle 5 and at the Treatment Discontinuation visit.
Blood for Plasma Biomarker Analyses			X	X			X				X				Samples should be obtained pre-dose of Cycle 1, Cycle 2, and Cycle 5 and at the Treatment Discontinuation visit.
Blood for Serum Biomarker Analyses			X	X			X				X				Samples should be obtained pre-dose of Cycle 1, Cycle 2, and Cycle 5 and at the Treatment Discontinuation visit.
Tumor Tissue Collection															
Archival or Newly Obtained Tumor Tissue collection	X														
On-Study Tumor Biopsy (Optional)				X											

Abbreviations: aPTT/PTT= activate; β-hCG=human chorionic gonadotropin; BID=twice daily; CBC=complete blood count; CEA= carcinoembryonic antigen; Discon=discontinuation; dMMR= deficient mismatch repair; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of trial; FBR=future biomedical research; FT3=free triiodothyronine; FT4=free thyroxine; IHC= immunohistochemistry; IV=intravenous; MSI/MMR= microsatellite instability/mismatch repair; MUGA= multigated acquisition; PCR= polymerase chain reaction; PK= pharmacokinetic; PT/INR = prothrombin time/International Normalized Ratio; prothrombin time/partial thromboplastin time; Q8W=every 8 weeks; Q9W=every 9 weeks; Q12W= every 12 weeks; QTc =Q-T interval; RNA=ribonucleic acid; TSH=thyroid stimulating hormone.

a. All screening laboratory tests should be performed within 10 days prior to the first dose of trial treatment.

2.2 Pembrolizumab in Combination with mFOLFOX7 (Cohort B)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	±3	±3	±3	±3	±7	±7	±14	
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for optional post-treatment tumor biopsy	X																					
Informed Consent for FBR (optional)	X																					
Participant Identification Card		X																				
Inclusion/Exclusion Criteria		X																				
Demographics and Medical History		X																				
Cancer disease status and Prior Treatment History		X																				
Prior and Concomitant Medication Review		X	X		X	X	X		X		X	X	X		X		X	X	X			Concomitant medication should be reviewed at every visit.
Pembrolizumab Administration			X			X			X			X			X							
mFOLFOX7 Administration			X		X		X		X		X		X		X	X	X					
Efficacy Assessments																						
Tumor Imaging		X	<==========X==========→															X		X		Tumor imaging at screening must be performed within 28 days prior to the date of Cycle 1 Day 1. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation. See Section 9.2.

Pembrolizumab in Combination with mFOLFOX7 (Cohort B)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Clinical Procedures/Assessments																						
Review adverse events		X	<==========X==========→															X	X	X		
Full Physical Exam		X																X				
Directed Physical Exam			X		X	X	X		X		X	X	X		X		X					
Height, Weight, and Vital Signs		X	X		X	X	X		X		X	X	X		X		X	X				Height will be measured at Visit 1 only.
12-Lead Electrocardiogram		X																				To be performed one time during screening using local standard procedures. Additional time points may be performed as clinically necessary.
ECOG PS		X	X			X			X			X			X			X				ECOG PS at screening to be assessed within 7 days prior to the first dose of trial treatment.
Post-Study Anticancer Therapy Status																				X	X	
Survival Status			<==========X==========→																		X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Local Laboratory Assessments																						
MSI/MMR Status	X																					If tumor testing is obtained by both PCR and IHC, the tumor result should be neither MSI-H by PCR nor dMMR by IHC to identify the non-MSI-H participants.

Pembrolizumab in Combination with mFOLFOX7 (Cohort B)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Pregnancy Test-Urine or Serum β-HCG		X	X																			Pregnancy tests may be performed if clinically warranted, or as defined by local regulations
PT/INR and aPTT		X																				
CBC with Differential[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			
Chemistry Panel[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			
Urinalysis[a]		X				X						X			X			X	X			To be performed at Screening, and every other cycle starting at Cycle 2.
T3 or FT3, FT4, and TSH		X				X						X			X			X	X			To be performed at screening, and every other cycle starting at Cycle 2.
Serum Tumor Marker			<==========X==========>															X	X			Serum tumor marker (CEA) to be collected Q3W.
Laboratory Procedures: Performed by Central Laboratory																						
Blood for Genetic Analyses			X																			To be collected pre-dose.
Blood for RNA Analyses			X			X									X			X				Blood sample for RNA analysis should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.
Blood for Plasma Biomarker Analyses			X			X									X			X				Blood sample for plasma should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.
Blood for Serum Biomarker Analyses			X			X									X			X				Blood sample for serum should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.

Pembrolizumab in Combination with mFOLFOX7 (Cohort B)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Tumor Tissue Collection																						
Archival and/or Newly Obtained Tissue Collection	X																					
Post-treatment Tumor Biopsy (Optional)						X																

Abbreviations: aPTT/PTT= activated prothrombin time/partial thromboplastin time; β-hCG=human chorionic gonadotropin; CBC=complete blood count; Discon=discontinuation; CEA= carcinoembryonic antigen; dMMR= deficient mismatch repair; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FBR=future biomedical research; FT3=free triiodothyronine; FT4=free thyroxine; IHC= immunohistochemistry; IV=intravenous; mFOLFOX7= (oxaliplatin [85 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2); MSI/MMR= microsatellite instability/mismatch repair MUGA= multigated acquisition; PCR= polymerase chain reaction; PS=performance score; PT/INR = prothrombin time/International Normalized Ratio;; Q9W=every 9 weeks; Q12W= every 12 weeks; RNA=ribonucleic acid; TSH=thyroid stimulating hormone.

a. All screening laboratory tests should be performed within 10 days prior to the first dose of trial treatment.

2.3 Pembrolizumab in Combination with mFOLFOX7 and Binimetinib (Cohort C)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for optional post-treatment tumor biopsy	X																					
Informed Consent for FBR (optional)	X																					
Participant Identification Card		X																				
Inclusion/Exclusion Criteria		X																				
Demographics and Medical History		X																				
Cancer disease status and Prior Treatment History		X																				
Prior and Concomitant Medication Review		X	X		X	X	X		X		X	X	X		X		X	X	X			
Pembrolizumab Administration			X			X			X			X			X							
Binimetinib Administration			<==========X==========→																			To be administered BID.
mFOLFOX7 Administration			X		X		X		X		X		X		X	X	X					
Efficacy Assessments																						
Tumor Imaging		X	<==========X==========→															X		X		Tumor imaging at screening must be performed within 28 days prior to the date of Cycle 1 Day 1. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation. See Section 9.2.

Pembrolizumab in Combination with mFOLFOX7 and Binimetinib (Cohort C)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Clinical Procedures/Assessments																						
Review adverse events		X	<==========X==========→															X	X	X		
Full Physical Examination		X																X				
Full Ophthalmic Examination (Q8W)	X					X			<==========X==========→									X				To be performed at screening, Cycle 2 Day 1 and then every 8 weeks (±7 days) from Cycle 2 Day 1 and EOT. An ophthalmic examination at the 30-day follow up is only required if there was a clinically significant abnormality noted at EOT (± 7 days)
Directed Physical Examination			X		X	X	X		X		X	X	X		X		X					
Height, Weight, and Vital Signs		X	X		X	X	X		X		X	X	X		X		X	X				Height will be measured at Visit 1 only.
12-Lead Electrocardiogram		X				X			X			X			X			X	X			ECG will be performed in triplicate to confirm QTc interval at screening. ECG will be performed predose starting at Cycle 2 Day 1.
Echocardiogram/MUGA scan (Q12W)	X					X									<=======X===→			X				ECHO/MUGA scans are to be performed at Screening, and pre-dose on Cycle 2 Day 1 and Cycle 5 Day 1, then every 12 weeks and EOT.
ECOG Performance Status		X	X			X			X			X			X			X				ECOG Performance Status at screening to be assessed within 7 days prior to the first dose of trial treatment.
Post-Study Anticancer Therapy Status																				X	X	

Pembrolizumab in Combination with mFOLFOX7 and Binimetinib (Cohort C)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Survival Status			<==========X==========→															X				After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Local Laboratory Assessments																						
MSI/MMR Status	X																					If tumor testing is obtained by both PCR and IHC, the tumor result should be neither MSI-H by PCR nor dMMR by IHC to identify the non-MSI-H participants.
Pregnancy Test-Urine or Serum β-HCG		X	X																			Pregnancy tests may be performed if clinically warranted, or as defined by local regulations.
PT/INR and aPTT		X																				
CBC with Differential[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			
Chemistry Panel[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			
Urinalysis[a]		X				X						X			X			X	X			To be performed at screening, and every other cycle starting at Cycle 2 Day 1.
T3 or FT3, FT4, and TSH		X				X						X			X			X	X			To be performed at Screening, and every other cycle starting at Cycle 2 Day 1.
Serum Tumor Marker			<==========X==========>															X	X			Serum tumor marker (CEA) to be collected Q3W.

Pembrolizumab in Combination with mFOLFOX7 and Binimetinib (Cohort C)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days)	-42 to -29	-28 to -1																				
Laboratory Procedures Performed by Central Laboratory																						
Blood for Genetic Analyses			X																			Collect pre-dose.
Blood for RNA Analyses			X			X									X			X				Blood sample for RNA analysis should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit
Blood for Plasma Biomarker Analyses			X			X									X			X				Blood sample for plasma should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.
Blood for Serum Biomarker Analyses			X			X									X			X				Blood sample for serum should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.
Tumor Tissue Collection																						
Archival and/or Newly Obtained Tissue Collection	X																					
Post-treatment Tumor Biopsy (Optional)						X																

Pembrolizumab in Combination with mFOLFOX7 and Binimetinib (Cohort C)

Abbreviations: aPTT/PTT= activated prothrombin time/partial thromboplastin time; β-hCG=human chorionic gonadotropin; CBC=complete blood count; CEA= carcinoembryonic antigen; Discon=discontinuation; dMMR= deficient mismatch repair; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT= end of trial; FBR=future biomedical research; FT3=free triiodothyronine; FT4=free thyroxine; IHC= immunohistochemistry; IV=intravenous; mFOLFOX7= (oxaliplatin [85 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2); MSI/MMR= microsatellite instability/mismatch repair MUGA= multigated acquisition; PCR= polymerase chain reaction; PT/INR = prothrombin time/International Normalized Ratio; Q8W=every 8 weeks; Q9W=every 9 weeks; Q12W= every 12 weeks; QTc =Q-T interval; RNA=ribonucleic acid; TSH=thyroid stimulating hormone.

a. All screening laboratory tests should be performed within 10 days prior to the first dose of trial treatment.

2.4 Pembrolizumab in Combination with FOLFIRI (Cohort D)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment																Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	±3	±3	±3	±3	±3	±7	±7	±14	
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for optional post-treatment tumor biopsy	X																					
Informed Consent for FBR (optional)	X																					
Participant Identification Card		X																				
Inclusion/Exclusion Criteria		X																				
Demographics and Medical History		X																				
Cancer disease status and Prior Treatment History		X																				
Prior and Concomitant Medication Review		X	X		X	X	X		X		X	X	X		X		X	X	X			
Pembrolizumab Administration			X			X			X			X			X							
FOLFIRI Administration			X		X		X		X		X		X		X	X	X					
Efficacy Assessments																						
Tumor Imaging		X	<==========X==========→															X		X		Tumor imaging at screening must be performed within 28 days prior to the date of Cycle 1 Day 1. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation. See Section 9.2.

Pembrolizumab in Combination with FOLFIRI (Cohort D)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Clinical Procedures/Assessments																						
Review adverse events		X	<==========X==========→															X	X	X		
Full Physical Examination		X																X				
Directed Physical Examination			X		X	X	X		X		X	X	X		X		X					
Height, Weight, and Vital Signs		X	X		X	X	X		X		X	X	X		X		X	X				Height will be measured at Visit 1 only.
12-Lead Electrocardiogram		X																				ECG will be performed one time during screening using local standard procedures. Additional time points may be performed as clinically necessary.
ECOG Performance Status		X	X			X			X			X			X			X				ECOG Performance Status at screening to be assessed within 7 days prior to the first dose of trial treatment.
Post-Study Anticancer Therapy Status																				X	X	
Survival Status			<==========X==========>															X				After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Local Laboratory Assessments																						
MSI/MMR Status	X																					If tumor testing is obtained by both PCR and IHC, the tumor result should be neither MSI-H by PCR nor dMMR by IHC to identify the non-MSI-H participants.

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															Discon	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon				Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Pregnancy Test-Urine or Serum β-HCG		X	X																			Pregnancy tests may be performed if clinically warranted, or as defined by local regulations.
PT/INR and aPTT		X																				
CBC with Differential[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			

Pembrolizumab in Combination with FOLFIRI (Cohort D)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Chemistry Panel[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			
Urinalysis[a]		X				X						X			X			X	X			To be performed at screening, and every other cycle starting at Cycle 2 Day 1.
T3 or FT3, FT4, and TSH		X				X						X			X			X	X			To be performed at screening, and every other cycle starting at Cycle 2 Day 1.
Serum Tumor Marker			<==========X==========>															X	X			Serum tumor marker (CEA) to be collected Q3W.
Laboratory Procedures: Performed by Central Laboratory																						
Irinotecan and SN-38 Pharmacokinetics					X																	Serial plasma samples for irinotecan and its active metabolite (SN-38) will be collected before (pre-infusion), the end of infusion, 1, 1.5, 2, 4, 6 (all ±10 min), 24 ± 2 hrs and 48 ± 2 hrs after the initiation of infusion in Cohort D. If irinotecan infusion time is between 45 minutes and 1 hour, then 1-hour sample is not needed, but all other time points apply. Irinotecan and SN-38 will be measured in the same sample.
Blood for Genetic Analyses			X																			To be collected pre-dose.
Blood for RNA Analyses			X			X									X			X				Blood sample for RNA analysis should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.
Blood for Plasma Biomarker Analyses			X			X									X			X				Blood sample for plasma should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.

Pembrolizumab in Combination with FOLFIRI (Cohort D)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Blood for Serum Biomarker Analyses			X			X									X			X				Blood sample for serum should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.
Tumor Tissue Collection																						
Archival and/or Newly Obtained Tissue Collection	X																					
Post-treatment Tumor Biopsy (Optional)						X																

Abbreviations: β-hCG=human chorionic gonadotropin; CBC=complete blood count; CEA= carcinoembryonic antigen; Discon=discontinuation; dMMR= deficient mismatch repair; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FBR=future biomedical research; FOLFIRI=(irinotecan [180 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2); FT3=free triiodothyronine; FT4=free thyroxine; IV=intravenous; IHC= immunohistochemistry; MSI/MMR= microsatellite instability/mismatch repair; MUGA= multigated acquisition; PCR= polymerase chain reaction; PT/INR = prothrombin time/International Normalized Ratio; aPTT/PTT= activated prothrombin time/partial thromboplastin time; Q9W=every 9 weeks; Q12W= every 12 weeks; RNA=ribonucleic acid; TSH=thyroid stimulating hormone.

a. All screening laboratory tests should be performed within 10 days prior to the first dose of trial treatment.

2.5 Pembrolizumab in Combination with FOLFIRI and Binimetinib (Cohort E)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment																Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for optional post-treatment tumor biopsy	X																					
Informed Consent for FBR (optional)	X																					
Participant Identification Card		X																				
Inclusion/Exclusion Criteria		X																				
Demographics and Medical History		X																				
Cancer disease status and Prior Treatment History		X																				
Prior and Concomitant Medication Review		X	X		X	X	X		X		X	X	X		X		X	X	X			
Pembrolizumab Administration			X			X			X			X			X							
Binimetinib Administration			<=========X=========→																			To be administered BID.
FOLFIRI Administration			X		X		X		X		X		X		X	X	X					
Efficacy Assessments																						
Tumor Imaging		X	<=========X=========→															X		X		Tumor imaging at screening must be performed within 28 days prior to the date of Cycle 1 Day 1. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation. See Section 9.2.

Pembrolizumab in Combination with FOLFIRI and Binimetinib (Cohort E)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment															End of Treatment	Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Clinical Procedures/Assessments																						
Review adverse events		X	<==========X==========→															X	X	X		
Full Physical Examination		X																X				
Full Ophthalmic Examination (Q8W)	X					X			<==========X==========→									X				To be performed at screening, Cycle 2 Day 1 and then every 8 weeks (±7 days) from Cycle 2 Day 1 and EOT. An ophthalmic examination at the 30-day follow up is only required if there was a clinically significant abnormality noted at EOT (±7 days)
Directed Physical Examination			X		X	X	X		X		X	X	X		X		X					
Height, Weight, and Vital Signs		X	X		X	X	X		X		X	X	X		X		X	X				Height will be measured at Visit 1 only.
12-Lead Electrocardiogram		X				X			X			X			X			X	X			ECG will be performed in triplicate to confirm QTc interval at screening. ECG will be performed predose starting at Cycle 2 Day 1.
Echocardiogram/MUGA scan (Q12W)	X					X									<======X===→			X				ECHO/MUGA scans are to be performed at Screening, and pre-dose on Cycle 2 Day 1 and Cycle 5 Day 1, then every 12 weeks and EOT.
ECOG Performance Status		X	X			X			X			X			X			X				ECOG Performance Status at Screening to be assessed within 7 days prior to the first dose of trial treatment.
Post-Study Anticancer Therapy Status																				X	X	

Pembrolizumab in Combination with FOLFIRI and Binimetinib (Cohort E)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment																Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 14	
Survival Status			==========X==========															X			X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Local Laboratory Assessments																						
MSI/MMR Status	X																					If tumor testing is obtained by both PCR and IHC, the tumor result should be neither MSI-H by PCR nor dMMR by IHC to identify the non-MSI-H participants.
Pregnancy Test-Urine or Serum β-HCG		X	X																			Pregnancy tests may be performed if clinically warranted, or as defined by local regulations.
PT/INR and aPTT		X																				
CBC with Differential[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			
Chemistry Panel[a]		X	X		X	X	X		X		X	X	X		X		X	X	X			
Urinalysis[a]		X				X						X			X			X	X			To be performed at screening, and every other cycle starting at Cycle 2 Day 1.
T3 or FT3, FT4, and TSH		X				X						X			X			X	X			To be performed at Screening, and every other cycle starting at Cycle 2 Day 1.
Serum Tumor Marker			<==========X==========>															X	X			Serum tumor marker (CEA) to be collected Q3W.

Pembrolizumab in Combination with FOLFIRI and Binimetinib (Cohort E)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment																Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Laboratory Procedures: Performed by Central Laboratory																						
Binimetinib Pharmacokinetics					X																	PK samples will be collected at time 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6 hrs (all ±10 min) on Day 15, pre-dose (24 ± 2 hrs from the first binimetinib PK collection) on Day 16 and pre-dose (48 ± 2 hrs from the first binimetinib PK collection) on Day 17 at Cycle 1. The exact time of sample collection and time of administration of binimetinib will be recorded. Only 1 sample is collected at each time point to measure concentrations of binimetinib, irinotecan and SN-38.
Irinotecan and SN-38 Pharmacokinetics					X																	Serial plasma samples for irinotecan and its active metabolite (SN-38) will be collected before (pre-infusion), the end of infusion, 1, 1.5, 2, 4, 6 (all ±10 min), 24 ± 2 hrs and 48 ± 2 hrs after the initiation of infusion. If irinotecan infusion time is between 45 min and 1 hour, then 1-hour sample is not needed, but all other time points apply. Irinotecan and SN-38 will be measured in the same sample.
Blood for Genetic Analyses			X																			To be collected pre-dose.
Blood for RNA Analyses			X			X									X			X				Blood sample for RNA analysis should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment																Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Blood for Plasma Biomarker Analyses			X			X									X			X				Blood sample for plasma should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.
Blood for Serum Biomarker Analyses			X			X									X			X				Blood sample for serum should be obtained pre-dose of Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1 and at the Treatment Discontinuation visit.

Pembrolizumab in Combination with FOLFIRI and Binimetinib (Cohort E)

Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles) End of Treatment																Post- Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)		1			2			3			4			5 to 35 Discon			Discon	Safety Follow Up	Follow-up Visits	Survival Follow up	
Treatment Days:			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	At time of Treatment discon	30 days Post last dose	Q9W Post-discon	Q12W	
Scheduling Window (Days):	-42 to -29	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14	
Tumor Tissue Collection																						
Archival and/or Newly Obtained Tissue Collection	X																					
Post-treatment Tumor Biopsy (Optional)						X																

Abbreviations: aPTT/PTT= activated prothrombin time/partial thromboplastin time; β-hCG=human chorionic gonadotropin; BID=twice daily; CBC=complete blood count; CEA= carcinoembryonic antigen; Discon=discontinuation; dMMR= deficient mismatch repair; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT= end of trial; FBR=future biomedical research; FOLFIRI=(irinotecan [180 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2); FT3=free triiodothyronine; FT4=free thyroxine; IHC= immunohistochemistry; IV=intravenous; MSI/MMR= microsatellite instability/mismatch repair; MUGA= multigated acquisition; PCR= polymerase chain reaction; PT/INR = prothrombin time/International Normalized Ratio; Q8W=every 8 weeks; Q9W=every 9 weeks; Q12W= every 12 weeks; QTc =Q-T interval; RNA=ribonucleic acid; TSH=thyroid stimulating hormone.

a. All screening laboratory tests should be performed within 10 days prior to the first dose of trial treatment.

3. Introduction

Metastatic colorectal cancer continues to be a serious, life-threatening condition. In the US, it is the fourth most common type of cancer with approximately 130,000 new cases projected in 2015, and it is the second leading cause of cancer mortality with nearly 50,000 projected deaths in 2015 [Siegel, R. L., et al 2015]. Standard therapy in patients with unresectable mCRC includes combination regimens with cytotoxic and targeted agents.

Despite recent advances, the intent of treatment for most of mCRC participants is palliative with few patients achieving long-term survival (5-year survival rate of 13.5%) [Centers for Disease Control and Prevention 2015]. Current SOC treatments for mCRC in the early-line setting include chemotherapy based on fluoropyrimidine, oxaliplatin, and irinotecan used in combination or sequentially, with option for monoclonal antibodies targeting VEGF (eg, bevacizumab, ziv-aflibercept) or its receptors (eg, ramucirumab) and in patients with Ras wild-type tumors, monoclonal antibodies targeting the EGF receptor (eg, cetuximab, panitumumab). Although the ORR reported in early line studies ranged from 31% to 60%, the DOR was limited (7.1 - 10.4 months) [Comella, P., et al 2009] [Diaz-Rubio, E., et al 2007] [Ducreux, M., et al 2011] [Porschen, R., et al 2007] [National Comprehensive Cancer Network 2015] [Colucci, G., et al 2005] [Tournigand, C., et al 2004] [Douillard, J. Y., et al 2010] [Hurwitz, H., et al 2004] [Van Cutsem, E., et al 2015] [Heinemann, V., et al 2014]. Ultimately, nearly all patients will require salvage therapies which have limited clinical benefit coupled with high toxicity. The ORR in the 2L setting for combination regimens (fluoropyrimidine plus oxaliplatin or irinotecan +/- anti-VEGF or anti-EGFR) is less than 23% while durations of benefit are limited (median PFS ≤ 7 months) [Van Cutsem, E., et al 2012] [Bennouna, J., et al 2013] [Tabernero, J., et al 2015] [Giantonio, B. J., et al 2007] [Iwamoto, S., et al 2015] [Masi, G., et al 2015] [Rothenberg, M. L., et al 2008].

Treatment options for heavily pre-treated patients beyond the 2L setting are limited and associated toxicities can be severe. Although regorafenib and TAS-102 are the 2 commonly accepted SOC therapies for patients who have been treated with fluoropyrimidine-, irinotecan-, oxaliplatin-containing chemotherapies, anti-VEGF and an anti-EGFR agent (if KRAS wild-type) offer minimal benefits as ORR is ≤2% for both agents [Grothey, A., et al 2013] [U.S. Prescribing Information 2012]. Minimal durability of clinical benefit is evidenced by a 6-month PFS rate of ~15%. Clearly, there is a high unmet medical need in developing novel combination regimens to improve the clinical outcome for patients with mCRC.

3.1 Study Rationale

3.1.1 Rationale for the Trial and Selected Participant Population

Pembrolizumab and other anti- PD1 agents produced durable clinical benefit in patients with mCRC with the dMMR/MSI-H phenotype [Le, D. T., et al 2015]. In the heavily treated mCRC setting, pembrolizumab produced high ORR as well as evidence for durable clinical benefit [Le, D. T., et al 2015]. However, anti-cancer activity in the CRC population has been limited to cancers with the dMMR/MSI-H phenotype, which represents a minority (~5%) of the Stage IV mCRC population.

Given that approximately 95% of mCRC patients have tumors that are non-microsatellite instability high (non-MSI-H/ pMMR), there is a need to develop combination regimens that would provide durable clinical benefit of immunotherapy such as pembrolizumab. While high response rates are reported in previously untreated mCRC population with current standard therapies, durability of clinical benefit is limited. Further, prognosis is poor when patients experience progression of disease after the initial treatment with combination chemotherapy. Given that durable clinical benefit is the hallmark of pembrolizumab demonstrated in multiple tumor types, addressing resistance to pembrolizumab in non-MSI-H population could improve the clinical outlook.

Emerging data suggest that combining PD1/PD-L1 inhibitors with other agents might sensitize tumors to immunotherapy and/or provide additive efficacy [Weinstock, M. 2015] [Bever, K. M. 2017]. Consequently, this trial is designed to assess safety, tolerability, PK, and explore preliminary efficacy in the following combinations in participants with non MSI-H/pMMR mCRC:

- Cohort A: Pembrolizumab in combination with binimetinib in mCRC participants previously treated with fluoropyrimidine, irinotecan, and oxaliplatin
- Cohort B: Pembrolizumab in combination with mFOLFOX7 in previously untreated mCRC participants
- Cohort C: Pembrolizumab in combination with mFOLFOX7 and binimetinib in previously untreated mCRC participants
- Cohort D: Pembrolizumab in combination with FOLFIRI in mCRC participants previously treated with one line of a fluoropyrimidine plus oxaliplatin-based regimen
- Cohort E: Pembrolizumab in combination with FOLFIRI and binimetinib in mCRC participants previously treated with one line of a fluoropyrimidine plus oxaliplatin-based regimen

3.1.2 Rationale for Cohort A: Pembrolizumab in Combination with Binimetinib in Previously-treated non-MSI-H/pMMR mCRC Population

Preclinical data show that the combination of a MEK inhibitor and an anti-PD1 agent results in superior tumor growth inhibition relative to anti-PD1 or MEK inhibitor alone [Morrissey, K. M., et al 2016] [Vella, L. J., et al 2014]. Recently, published data suggest that combining a MEK inhibitor with an anti-PD1 agent can produce anti-tumor responses in non-MSI-H mCRC patients [Bendell, J. C., et al 2016].

The proposed mechanisms are:

- MEK inhibition increases the number of active immune cells (eg, CD8+ cells) in the tumor.
- MEK inhibition reduces the expression of immune suppressive factors in the tumor microenvironment.
- MEK inhibition results in tumor cell killing leading to release of tumor antigen.

Recent clinical data supporting this hypothesis were presented at the ASCO meeting in 2016 [Bendell, J. C., et al 2016]. Atezolizumab (a PD-L1 inhibitor) in combination with cobimetinib (a MEK inhibitor) produced a 17% ORR (N=23) with evidence of durable clinical benefit, 6-month PFS of 35%, and 6-month OS of 72% in heavily treated non-MSI-H mCRC [Bendell, J. C., et al 2016]. These data suggest possible synergy between 2 agents since MEK inhibitors (eg, cobimetinib, AZD6244, RO49887655, binimetinib) have shown 0% ORR in mCRC clinical trials and 0% ORR was reported with pembrolizumab [Le, D. T., et al 2016] and nivolumab [Overman, M. J., et al 2016] in non-MSI-H mCRC population. A correlative study suggested the proposed mechanism to be an increase in the number of intratumoral CD8+ T-cell infiltration and major histocompatibility complex 1 (MHC1) expression with cobimetinib [Bendell, J. C., et al 2016].

In the previously described Phase 1 dose escalating trial of atezolizumab and cobimetinib and in mCRC [Bendell, J. C., et al 2016], no dose-limiting toxicities were observed, and expansion occurred at atezolizumab 800 mg Q2W and cobimetinib 60 mg. Median follow-up for safety in CRC patients was 3.78 months (range, 1.1-11.7). The most common treatment-related AEs included diarrhea (69.6%), fatigue (52.2%), dermatitis acneiform (43.5%), rash (34.8%), maculopapular rash (26.1%), pruritus (26.1%) and nausea (26.1%). Incidence of treatment-related Grade 3-4 AEs was 34.8%. The only treatment-related Grade 3-4 AE in ≥ 2 patients was diarrhea (8.7%). No Grade 5 AEs were reported.

In summary, preclinical and clinical data suggest that addition of binimetinib may enable non-MSI-H/pMMR mCRC to be susceptible to pembrolizumab.

3.1.3 Rationale for Cohorts B and C: Combination of Pembrolizumab plus mFOLFOX7 With and Without Binimetinib in Previously Untreated Metastatic non MSI-H/pMMR mCRC Population

There is accumulating evidence demonstrating that chemotherapy agents including 5-FU and oxaliplatin that are commonly used to treat CRC may modulate the intrinsic immunogenicity of tumor and sensitize tumors to immunotherapy agents [Pfirschke, C., et al 2016] [Zhou, J., et al 2017]. Preclinical and clinical evidence suggest that conventional chemotherapies reactivate antitumor immune responses by increasing immunogenic cell death and antigen release, and/or by inhibiting immunosuppressive factors in the tumor microenvironment [Emens, L. A. 2015] [Galluzzi, L., et al 2015] [Vincent, J., et al 2010]. Further, chemotherapies can enhance tumor antigen presentation by upregulating the expression of tumor TCR themselves, or of the MHC1 molecules to which the TCRs bind [Emens, L. A. 2015].

Although there are multiple therapeutic options for untreated patients with CRC, the majority of patients still experience disease progression and/or succumb to the disease in less than a year and there are few long term survivors. As discussed below, a substantial body of scientific evidence has emerged to suggest that the efficacy of immunotherapy can be enhanced by chemotherapy such as fluorouracil (5-FU) and oxaliplatin. While KEYNOTE-651 (KN651) will investigate the combination of pembrolizumab and mFOLFOX7 in untreated CRC patients, both safety and efficacy will be carefully monitored, with a pre-defined efficacy futility criterion to ensure that expected efficacy in untreated patients is no worse than what would be expected with mFOLFOX7 alone.

Recently, preclinical and clinical evidence suggest that conventional chemotherapies reactivate antitumor immune responses by increasing immunogenic cell death and antigen release, and/or by inhibiting immunosuppressive factors in tumor microenvironment [Emens, L. A. 2015] [Galluzzi, L., et al 2015] [Vincent, J., et al 2010]. As such, chemotherapy agents may modulate the intrinsic immunogenicity of tumor and sensitize tumors to immunotherapy agents by upregulating the expression of tumor TCR or the MHC1 molecules, and subsequently enhancing tumor antigen presentation to CD8+ T cells [Emens, L. A. 2015]. For example, 5-FU can increase the frequency of TIL including CTLs, upregulate MHC1 on cancer cells and decrease immunosuppressive myeloid derived suppressor cells [Apetoh, L., et al 2015], while oxaliplatin can increase immunogenicity of cancer cells and induce immunogenic cell death [Tesniere, A., et al 2010]. Indeed, FOLFOX plus bevacizumab combined with atezolizumab demonstrated an acceptable safety profile and promising activity (ORR, 52%; median PFS, 14.1 months; DOR, 11.4 months) [Wallin, J., et al 2016]. This study clearly demonstrated increase of PD-L1 expression, enhanced intra tumoral infiltration CD8+ of T cells, and upregulation of immune gene signature in tumor by use of FOLFOX alone or in combination with atezolizumab [Wallin, J., et al 2016]. Further, there was an association between an increase in immune gene signature and durability of clinical benefit. Results from several clinical trials have demonstrated that chemotherapies can be safely combined with anti- PD1/PD-L1 agents with promising anti-cancer activity [Reck, M., et al 2016] [Langer, C. J., et al 2016] [Wallin, J., et al 2016].

An investigator-initiated, Phase II study (NCT02375672) was designed to evaluate the combination of pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W) and mFOLFOX6 in advanced untreated CRC patients. Updated data were presented at ASCO 2017 (data cutoff date of 01-MAY-2017). While this study utilizes mFOLFOX6, which is known to induce neutropenia in approximately 40% to 45% and neutropenic fever in approximately 2% to 5% of patients [Douillard, J. Y., et al 2010] [Cassidy, J., et al 2011], the dose limiting toxicity definition did not have provision for this known chemotherapy-related toxicity the in the protocol. During the run-in phase for the safety cohort of 6 patients, because 2 reported events of febrile neutropenia, the institutional Data Safety Monitoring Committee recommended dose reduction of mFOLFOX6 as per protocol. The study successfully completed enrolling an additional 24 patients who were treated with pembrolizumab 200 mg Q3W and dose reduced mFOLFOX6 with oxaliplatin 65 mg/m^2 IV, leucovorin 400 mg/m^2 IV, 5-FU 320 mg/m^2 IV bolus, then 5-FU 1920 mg/m^2 IV over 46 hours. At the median follow up of 34 weeks, the best objective response rate for the 30 patients was 40% (n = 30) and median PFS was 16.9 months, which appears promising in comparison with reported ORR of 46% and median PFS of 9.3 months for FOLFOX6 in untreated patients [Ducreux, M., et al 2011].

Results from several clinical trials have demonstrated that chemotherapies can be safely combined with PD-L1 agents and demonstrated promising anti-cancer activity [Reck, M., et al 2016] [Langer, C. J., et al 2016] [Wallin, J., et al 2016]. Various chemotherapies including pemetrexed and platinum were combined with pembrolizumab in NSCLC and produced promising activity in the previously untreated NSCLC population [Reck, M., et al 2016]. In KN-021, addition of pembrolizumab to carboplatin and pemetrexed showed superior PFS outcomes to carboplatin and pemetrexed without pembrolizumab (HR, 0.53; p=0.01) [Langer, C. J., et al 2016]. On the other hand, FOLFOX plus bevacizumab was combined

with atezolizumab and demonstrated an acceptable safety profile and promising activity (ORR, 52%; median PFS, 14.1 months; DOR, 11.4 months) [Wallin, J., et al 2016]. In this study, there was a clear demonstration of increase of PD-L1 expression, enhanced intra tumoral infiltration of CD8+ T cells, and upregulation of an immune gene signature in tumor by use of FOLFOX alone or in combination with atezolizumab [Wallin, J., et al 2016]. Further, there was an association between an increase in immune gene signature and durability of clinical benefit.

In summary, accumulating evidence suggest that chemotherapies, including agents used in mCRC population, may be combined with pembrolizumab and improve efficacy in IL treatment of mCRC. Together with the encouraging data from atezolizumab/cobimetinib mCRC study, adding MEK inhibitor binimetinib to pembrolizumab/mFOLFOX7 may further enhance patient outcomes in this setting without added toxicity. While safety will be carefully monitored in the study, a futility analysis will be conducted to ensure that expected efficacy in untreated patients is no worse than that expected with mFOLFOX7 treatment alone.

3.1.4 Rationale for Cohorts D and E: Combination of Pembrolizumab plus FOLFIRI With and Without Binimetinib in Previously-treated non MSI-H/pMMR mCRC Population

As previously discussed in Section 3.1.2, there is accumulating evidence demonstrating that chemotherapy agents including 5-FU and oxaliplatin that are commonly used to treat CRC may modulate the intrinsic immunogenicity of tumor and sensitize tumors to immunotherapy agents [Pfirschke, C., et al 2016] [Zhou, J., et al 2017]. Although evidence of similar immune-modulating effect and synergy from clinical studies is scant for irinotecan, FOLFIRI may potentially sensitize tumors to checkpoint inhibitors that its combination with anti-PD-1 warrants study in 2L treatment of mCRC because FOLFIRI is a commonly used regimen in this setting. A study involving 27 patients with mCRC who received FOLFOX (n=17) or FOLFIRI (n=10) showed that the percentage and the number of CD4(+)FoxP3(+) T-regs were significantly reduced after FOLFOX and FOLFIRI in the patients who had high levels of T-regs before chemotherapy, suggesting FOLFOX and FOLFIRI may enhance antitumor immunity via suppression of T-regs [Maeda, K., et al 2011]. On the other hand, the total number of lymphocytes and the population of CD4(+) T lymphocytes were unchanged. As discussed above in Section 3.1.2, the addition of binimetinib may sensitize non-MSI-H CRC to pembrolizumab. Therefore, the combination of FOLFIRI plus binimetinib may further change tumor microenvironment favorably for immunotherapy and sensitize non MSI-H CRC to pembrolizumab.

A Phase Ib study, PembroPlus, was one of the first reported multi-arm systemic chemotherapy study in combination with PD-1 inhibitors across diverse advanced solid tumors. Twelve patients (2 small-cell lung cancer, 8 NSCLC, 1 CRC, 1 gastric cancer) were treated with pembrolizumab 2 mg/kg and irinotecan 300 mg/m^2 Q3W. The only mCRC patient enrolled in this arm had PD. Overall this combination were associated with Grade 1-2 fatigue (41.7%), diarrhea (75%), nausea (75%), vomiting (33.3%), rash not otherwise specified (25%), and anorexia (25%), and Grade 3-4 neutropenia (25%). Immune-related adverse events (likely or definitely related) were reported in 33.3% of patients treated with

this combination. A Grade 3 rash and papilloedema was a DLT and led to a dose reduction [Weiss, G. J., et al 2017].

3.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. Refer to the pembrolizumab IB/approved labeling for detailed background information on pembrolizumab. Refer to the binimetinib IB for detailed background information on binimetinib. Also refer to the respective approved labeling for detailed background information on SOC chemotherapies.

3.2.1 Pharmaceutical and Therapeutic Background

3.2.1.1 Pembrolizumab Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ T-regs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene PDCD1) is an immunoglobulin superfamily member related to cluster of differentiation 28 (CD28) and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. Programmed death 1 and its family members are type 1 transmembrane glycoproteins containing an Ig variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade

[Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009] [Okazaki, T., et al 2001]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010].

3.2.1.1.1 Pembrolizumab Pre-clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma [Nomi, T., et al 2007] [Blank, C. and Mackensen, A. 2007] [Iwai, Y., et al 2002] [Pölcher, M., et al 2010] [Korman, A., et al 2007]. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon gamma, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [Ropponen, K. M., et al 1997]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the current version of the IB for further details).

3.2.1.1.2 Pembrolizumab Clinical Trials

Clinical trials have demonstrated efficacy in patients with metastatic melanoma, metastatic NSCLC, metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%), recurrent or metastatic HNSCC, bladder cancer, refractory classical Hodgkin lymphoma, and other tumor types.

Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune-mediated AEs are of primary concern. The important identified AEs for pembrolizumab are of an immune-mediated nature, and are: pneumonitis; colitis; hepatitis; nephritis; endocrinopathies that include hypophysitis, thyroid disorder, and Type I diabetes mellitus; uveitis; myositis; Guillain-Barré syndrome; pancreatitis; myocarditis; myasthenic syndrome; severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, some with fatal outcome; encephalitis, sarcoidosis, and "solid organ transplant rejection following pembrolizumab treatment in donor organ recipients". The majority of immune-mediated AEs were mild to moderate in severity, manageable with appropriate care, and rarely required discontinuation of therapy (see the current version of the IB for further details).

Based on safety data of pembrolizumab evaluated in 2799 patients in controlled and uncontrolled studies, the 5 most frequently reported AEs considered drug related by the investigator were fatigue, pruritus, rash, diarrhea, and nausea (see the current version of the IB for further details).

3.2.1.1.3 Pembrolizumab Ongoing Clinical Trials

Ongoing clinical trials with pembrolizumab are being conducted in multiple solid tumors. In addition, multiple combinations with pembrolizumab are also being investigated. Furthermore, there are several ongoing trials to investigate activity of pembrolizumab as

monotherapy and in combination with other agents in patients with mCRC. For trial details please refer to the current version of the IB.

3.2.1.2 Binimetinib Background

Binimetinib (also known as MEK162 or ARRY-438162) is a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK1/2 that is active in inhibiting pERK and growth of BRAF-mutant cancer cells in the low nanomolar range. In oncology settings, binimetinib is currently being investigated both as a single agent and in combination with RAF or PI3K or inhibitors in patients with selected advanced or metastatic solid tumors, including biliary cancer, CRC, and melanoma.

3.2.1.2.1 Binimetinib Pre-clinical Studies

Acute, subchronic, chronic and reproductive toxicity, genotoxicity, and phototoxicity studies were completed in rats and monkeys to support the chronic administration of binimetinib to adult patients. There was no evidence of a genotoxic potential in vitro or in vivo. The adverse effects of MEK inhibitors in humans are similar to those observed in rats and monkeys, with the exception of ocular findings. These adverse effects include gastro-intestinal intolerance and diarrhea, rash (skin findings in rats only), retinal events (only seen in humans) and RVO (rarely seen in humans). In vitro and in vivo phototoxicity studies conducted in mice indicate that binimetinib has a low risk of weak phototoxic potential at therapeutic doses. Furthermore, there has been no evidence of phototoxicity or photosensitivity in humans being treated with binimetinib for cancer or for rheumatoid arthritis.

Given the embryo-lethal effects seen in rats and rabbits and the teratogenic effects seen in rabbits, binimetinib should not be used in pregnant women. Women of child-bearing potential must be advised to use highly effective contraception methods.

For further details, please refer to the current binimetinib IB.

3.2.1.2.2 Binimetinib Clinical Studies

As of 20-JAN-2017, a total of 2750 healthy participants and patients have received at least 1 dose of binimetinib and are therefore eligible for inclusion in the overall safety population of binimetinib, which comprises 229 healthy participants, 164 patients with rheumatoid arthritis, 17 patients with hepatic dysfunction, 6 participants with renal dysfunction and 2334 patients with advanced cancer. Binimetinib demonstrated benefit over SOC agents in advanced melanoma as monotherapy as well as in combination with BRAF inhibitor [Ascierto, P. A., et al 2016] [Dummer, R., et al 2016] [Dummer, R., et al 2017]. The binimetinib clinical development program also includes ongoing trials in patients with mCRC including a Phase I trial investigating binimetinib in combination with mFOLFOX7 and a Phase I trial investigating binimetinib in combination with FOLFIRI.

In a Phase I dose-escalation study of oral binimetinib in patients with advanced solid tumors, common AEs (all grades) included combined rash, nausea, vomiting, diarrhea, peripheral edema, and fatigue. Ocular events were reported in 19% of patients. Most patients experienced Grade 2 (41%) or Grade 3 (49%) events. The most common Grade 3 events included anemia (11%), and abdominal pain and dehydration (4% each). Grade 4 AEs were reported for 6% of patients; those that occurred in at least 2 patients included anemia (3%).

There were no Grade 5 events. Laboratory abnormalities included increases in CPK and liver function tests [Bendell, J. C., et al 2017]. Of note, rash, ocular events, gastrointestinal events, increased CK, and edema are known class effects of MEK inhibitors [Larkin, J., et al 2014] [Bennouna, J., et al 2011] [Infante, J. R., et al 2012].

A Phase I trial was conducted to combine binimetinib and mFOLFOX7 in previously treated mCRC patients was recently presented [Thet Cho, M., et al 2016]. The study demonstrated that addition of 30 mg BID or 45 mg BID binimetinib was well tolerated without DLT in heavily treated mCRC participants; Treatment-related ≥ Grade 3 toxicities included anaphylaxis due to oxaliplatin (n=1), CPK elevation (n=2), neutropenia (n=1), peripheral neuropathy (n=3), thrombocytopenia (n=1), retinal vascular disorder (n=1), and acneiform rash (n=1). The combination showed promise in this heavily pretreated population who had been exposed to mFOLFOX7 before as 10/16 participants achieved stable disease at 2 months, 5 of whom with stabilizations of > 4 months (4-10 months). Similarly, there is an ongoing study where FOLFIRI is being combined with binimetinib; while study data are not yet mature [ClinicalTrials.gov 2017].

For further details, please refer to the current binimetinib IB.

3.2.1.3 FOLFOX as First Line Therapy

FOLFOX have been established as SOC 1L and 2L chemotherapy options for mCRC; however, FOLFOX is more frequently used in the 1L setting. Oxaliplatin combined with infusional 5-FU and leucovorin administered Q2W (FOLFOX) has been shown to be effective [Tournigand, C., et al 2004] and the mFOLFOX7 regimen is considered one of the SOC regimens for 1L treatment of mCRC [National Comprehensive Cancer Network 2017].

The most common AE overall was PSN (76.0%), followed by fatigue (70.9%), nausea (63.7%), diarrhea (53.6%), constipation (39.7%), and vomiting (31.3%); other AEs occurred in <30% of subjects. The most common SAE was neutropenia (16.7%), PSN (11.1%), diarrhea (8.3%), lymphopenia (2.8%), hypertension (2.8%), vomiting (2.8%), and fatigue (2.8%) [Hochster, H. S., et al 2014]. Neutropenia/neutropenic fever is a known toxicity associated with mFOLFOX6 chemotherapy and may be related to the 5-FU bolus for this regimen, which is known to be associated with myelosuppression. Hochster et al. reported 18.2% Grade 3/4 neutropenia with mFOLFOX7 (without 5-FU bolus), while FOLFOX regimens that contain 5-FU bolus reported significantly higher frequency of approximately 44% to 47% [Hochster, H. S., et al 2014] [Cassidy, J., et al 2011] [Douillard, J. Y., et al 2010]. For this reason in KN651, Sponsor elected to use the mFOLFOX7 regimen, which lacks a 5-FU bolus and is associated with less neutropenia than mFOLFOX6.

3.2.1.4 FOLFIRI as Second Line Therapy

FOLFIRI have been established as SOC 1L and 2L chemotherapy options for mCRC. However, FOLFIRI is more frequently used in the 2L setting after oxaliplatin-based 1L therapies. Irinotecan combined with infusional 5-FU and leucovorin administered Q2W (FOLFIRI) has been shown to be more effective than when irinotecan is combined with bolus 5-FU [Fuchs, C. S., et al 2007]. The regimen is considered one of the SOC regimens in 2L mCRC [National Comprehensive Cancer Network 2017] and has also been shown to be effective in previously untreated patients [Bekaii-Saab, T. 2014]. For example, in the randomized Phase II/III FIRIS study comparing FOLFIRI vs irinotecan/S-1 (IRIS) in 2L

treatment of mCRC, FOLFIRI was associated with ORR of 16.7% and median PFS of 5.1 months. The incidence of Grade 3 or 4 neutropenia was 52.1%. The most common non-hematological toxicities were diarrhea (4.7%), anorexia (5.2%), nausea (4.3%), fatigue (3.3%), and febrile neutropenia (0.9%), all at Grade 3. One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment [Muro, K., et al 2010].

3.3 Benefit/Risk Assessment

Participants in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants participating in this clinical trial may be found in the accompanying binimetinib and pembrolizumab IB, in the respective product labeling for SOC chemotherapy, and in the Informed Consent documents.

Given the unmet medical need that exists for patients with mCRC, described in Section 3.1, the objective of the current trial is to assess safety and tolerability of 5 different novel combinations that includes pembrolizumab. Extended duration of clinical benefit coupled with favorable tolerability and toxicity have been the hallmark of pembrolizumab in many tumor types including MSI-H/pMMR mCRC. Combination regimens being examined in the current trial have a potential to provide improvement of efficacy without increase of toxicity.

3.3.1 Potential Overlapping Toxicities

The combination of pembrolizumab with binimetinib and/or chemotherapy proposed in this protocol potentially may increase overlapping toxicities, and the potential overlapping toxicities for each cohort is presented in Table 1. The most likely overlapping toxicities are described in detail below.

Table 1 Potential Overlapping Toxicities for Each Cohort

	Pembrolizumab +				
Adverse Event	**Binimetinib**	**mFOLFOX7**	**mFOLFOX7 + Binimetinib**	**FOLFIRI**	**FOLRIRI + Binimetinib**
Diarrhea	✓	✓	✓	✓	✓
Nausea	✓		✓		✓
Vomiting	✓	✓	✓	✓	✓
Neutropenia		✓	✓		
Peripheral sensory neuropathy		✓	✓		
Rash	✓		✓		✓
Ocular toxicity	✓		✓		✓
Liver test abnormalities	✓		✓		✓
Pneumonitis	✓		✓		✓

Sections 5.4.1.3, 6.2, 7.2.1, 9.3, and 12.5 provide guidance, requirements, and mitigation strategies to minimize the possibility of overlapping toxicities.

3.3.1.1 Pneumonitis

In pooled studies of pembrolizumab, all grade pneumonitis as irAE was reported in 3.4% patients (among which 0.1% were Grade 5), and it is the most frequently reported SAEs considered drug-related by the investigator was pneumonitis (1.6%). In the pooled studies of single-agent binimetinib in patients with advanced cancer (N = 566), pneumonitis events were observed in 15 (2.7%) patients. No individual preferred term was reported for >1.0% of patients, and pneumonitis was the most common event (0.9%). Grade 3/4 pneumonitis events were reported for 4 (0.7%) patients, including pneumonitis, hypoxia, interstitial lung disease, and wheezing. Pneumonitis events were SAEs for 5 (0.9%) patients and resulted in binimetinib discontinuation for 2 (0.4%) patients (MEK162 IB Version 14). Thus, combining pembrolizumab and binimetinib may increase incidence or severity of pneumonitis in participants to be treated in Cohort A. Rare cases of pulmonary toxicities including pneumonitis, organizing pneumonia, pulmonary fibrosis, and interstitial lung disease have been reported with FOLFOX or FOLFIRI treatment [Lee, Y. J. 2014] [Moskovitz, M. 2015] [Katsuta, E. 2011]. Thus, early recognition of pneumonitis and initiation of systemic corticosteroids is critical to reduce the risk of complications.

3.3.1.2 Liver Test Abnormalities

In pooled studies of pembrolizumab, Grade 2-4 hepatitis as irAE was reported in 0.7% patients. Autoimmune hepatitis is the fifth most frequently reported SAEs (0.3%) considered drug-related by the investigator (pembrolizumab current IB). In the pooled studies of single-agent binimetinib in patients with advanced cancer (N = 566), incidence of AST increased and ALT increased were 14.8% and 10.8%, respectively. Grade 3/4 liver events were reported for 6.9% of subjects, including AST increased (3.0%), ALT increased (2.3%), gamma glutamyl transferase increased (1.6%), INR increased (0.7%), ascites (0.5%), blood bilirubin increased and hyperbilirubinemia (0.4% each), and acute hepatic failure, hepatic failure, hepatic function abnormal, hepatic pain and liver injury (0.2% each; binimetinib IB). On the other hand, 5-FU, a thymidylate synthetase inhibitor, when given intravenously, is not only converted in tissues to its active form, 5-fluoro-deoxyuridine-monophosphate, but also catabolized, primarily in the liver, by the dihydrouracil dehydrogenase and then cleaved to α-fluoro-β-alanine, ammonia, urea and carbon dioxide, as in the degradation of uracil. In spite of this well-known liver-mediated catabolism, only mild hepatotoxicity and steatosis have been reported when the drug is given intravenously [Peppercorn, P. D. 1998]. The active metabolite of irinotecan, SN-38, is inactivated by glucuronidation in the liver and can lead to steatosis [Robinson, S. M., et al 2012]. Thus, combination of 5-FU with irinotecan potentially can cause overlapping liver toxicity; however, it is not a common AE associated with FOLFIRI in CRC patients [Vincenzi, B., et al 2015] [Peeters, M. 2015]. In summary, liver test abnormalities or liver toxicities may occur as potential overlapping toxicity in any of the drug combinations proposed in this study, and will be closely monitored. For suspected autoimmune hepatitis, investigators are required to treat with systemic corticosteroids per Table 6 of the protocol, as specified in protocol Section 7.2.1.2, in addition to appropriate diagnostic tests and supportive care.

3.3.1.3 Diarrhea

Diarrhea is a common AE related to mFOLFOX7, FOLFIRI, binimetinib, and pembrolizumab. In addition, colitis and diarrhea reported as drug-related SAE by the investigator were 0.9%, and 0.6%, respectively, in patients treated with pembrolizumab. The incidence of diarrhea may increase in any of these drug combinations. Thus, all diarrhea events will be closely monitored. For suspected immune related colitis, investigators are required to adequately evaluate and confirm etiology or exclude other causes, and treat with systemic corticosteroids per Table 6 of the protocol, as specified in protocol Section 7.2.1.2. Additional procedures or tests such as colonoscopy and biopsy may be included as part of the evaluation. Supportive care is outlined in Section 7.7.1 and Table 8 of the protocol.

3.3.2 Other Risks

The addition of pembrolizumab and binimetinib may cause toxicities that require dose reduction, interruption and or discontinuation of the approved drugs (mFOLFOX7/FOLFIRI) which have been demonstrated to provide benefit to participants.

4. Objectives/Hypotheses and Endpoints

The objectives and endpoints apply to the study population of adult male and female participants with non-MSI-H/pMMR mCRC.

Objective/Hypothesis	Endpoint
Primary	

Objectives:
• To determine the safety and tolerability and to establish a preliminary RP2D for the following cohorts:
  ○ Cohort A: (pembrolizumab in combination with binimetinib in mCRC participants previously treated with fluoropyrimidine, irinotecan, and oxaliplatin).
  ○ Cohort B: (pembrolizumab in combination with mFOLFOX7 in previously untreated mCRC participants)
  ○ Cohort C: (pembrolizumab in combination with mFOLFOX7 and binimetinib in previously untreated mCRC participants).
	• Determined by incidence of DLTs

Objective/Hypothesis	Endpoint
○ Cohort D: (pembrolizumab in combination with FOLFIRI in mCRC participants previously treated with one line of a fluoropyrimidine plus oxaliplatin-based regimen). ○ Cohort E: (pembrolizumab in combination with FOLFIRI and binimetinib in mCRC participants previously treated with one line of fluoropyrimidine plus oxaliplatin-based regimen)	
Secondary	
• To evaluate the ORR based on RECIST 1.1 as assessed by the investigator for each cohort	• (ORR, defined as the proportion of participants in the analysis population who experience CR or PR as assessed by the investigator based on RECIST Version 1.1.
Tertiary/Exploratory	
• To evaluate serum levels of protein biomarkers (eg, CEA) before and after administration of pembrolizumab in combination with chemotherapy and/or binimetinib for each cohort	• Determination of molecular/proteomic markers indicative of clinical response, safety or mechanism of action of pembrolizumab and other study treatments
• To evaluate the DOR, DCR, PFS based on RECIST 1.1 as assessed by the investigator and OS for each cohort	• DOR, defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first, as assessed by the investigator per RECIST 1.1 criteria. • DCR, defined as and the percentage of participants who have achieved CR or PR or have demonstrated SD prior to any evidence of progression as assessed by the investigator per RECIST 1.1 criteria. • PFS, defined as the time from allocation to the first documented disease progression or death due to any cause, whichever occurs first, as assessed by the investigator based on RECIST Version 1.1 • OS, defined as the time from the date of allocation to the date of death due to any cause.

Objective/Hypothesis	Endpoint
• To evaluate the DOR, ORR, DCR, and PFS based on iRECIST as assessed by the investigator for each cohort	• DOR, ORR, DCR, and PFS as assessed by the investigator per iRECIST 1.1 criteria
• To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab in combination with chemotherapy and/or binimetinib for each cohort	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other blood-derived biomarkers • Tumor RNA immune cell activation and MHC molecule expression, proteomics and IHC to assess immune cells (CD8 T cell) infiltration, proliferation, and activation
• To explore the effects of binimetinib on the pharmacokinetics of irinotecan and SN-38, conversely, to estimate the effects of irinotecan and SN-38 on the PK of binimetinib for participants in Cohort A, D, and E	• Blood samples of binimetinib, irinotecan and SN-38 will be obtained to measure PK of binimetinib, irinotecan, and SN-38, and appropriate methods will be applied to assess the PK interactions.

5. Study Design

5.1 Overall Design

This is a multicenter, worldwide, open label, non-randomized, Phase 1b trial of pembrolizumab in combination with chemotherapy and/or MEK inhibitor binimetinib in participants with a histologically confirmed diagnosis of mCRC (Stage IV) that are non-MSI-H or pMMR. This trial includes 2 parts: Part 1 will be a dose finding phase and Part 2 will be a dose confirmation phase to further examine safety and explore efficacy. There are a total of 5 cohorts. Each of the 5 cohorts will participate in Part 1 and Part 2. The study will evaluate safety, tolerability and efficacy in the following 5 cohorts that will enroll participant with non-MSI-H/pMMR mCRC:

- Cohort A: Pembrolizumab in combination with binimetinib in mCRC participants previously treated with fluoropyrimidine, irinotecan, and oxaliplatin
- Cohort B: Pembrolizumab in combination with mFOLFOX7 in previously untreated mCRC participants
- Cohort C: Pembrolizumab in combination with mFOLFOX7 and binimetinib in previously untreated mCRC participants
- Cohort D: Pembrolizumab in combination with FOLFIRI in mCRC participants previously treated with one line of a fluoropyrimidine plus oxaliplatin-based regimen

- Cohort E: Pembrolizumab in combination with FOLFIRI and binimetinib in mCRC participants previously treated with one line of fluoropyrimidine plus oxaliplatin-based regimen

There is no intent to compare Cohorts B and C or Cohorts D and E. Each cohort will have independent objectives and will be analyzed separately.

The MSI or MMR status must be known prior to enrollment and the participants must be non MSI-H (or pMMR). Local documentation of non MSI-H/pMMR status using one method ie, IHC or PCR will be sufficient to meet eligibility criteria, as defined in Section 5.4.1.6 to be eligible for this study.

Pre-treatment tumor tissue is required to be provided prior to allocation into the study. If not available, a tumor biopsy must be obtained prior to entry in the study.

In both parts of the trial, participants will be allocated using an IVRS/IWRS. Pembrolizumab (200 mg) will be administered by IV infusion on Day 1 of each 21-day cycle; the dose of pembrolizumab will remain constant for all cohorts. Chemotherapy (mFOLFOX7 and FOLFIRI) will be administered by IV infusion every 14 days. Binimetinib will be administered orally BID. For additional details on study treatment administration, please see Section 7.1.

5.1.1 Study Design

5.1.1.1 Part 1 (Dose Finding)

An mTPI design [Ji Y, Li Y, Bekele BN 2007] with a target DLT rate of approximately 30% will be applied to identify a preliminary RP2D in each cohort.

Dose escalation and de-escalation decisions are based on the mTPI design as outlined in Table 1.

For **Cohort A**, the DLT observation period is the first **21-days** of Cycle 1 and the next dose level may open for enrollment once the 21-days DLT observation period of the previous dose is completed and a dose escalation decision is made.

For **Cohorts B, C, D, and E**, the DLT observation period is the first **28-days** to accommodate the chemotherapy schedule and the next dose level may open for enrollment once the 28-days DLT observation period of the previous dose is completed and a dose decision (escalation or de-escalation) is made.

During dose finding, a minimum of 3 participants are required at each dose level, and up to 6 participants may be enrolled in the same cycle at each new dose. In Table 2, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing DLT. The entries in the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the trial due to unacceptable toxicity, respectively.

Based on the mTPI design, the number of participants who are enrolled at a dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining participants who are at risk of developing a DLT before the dose would be considered unacceptably toxic

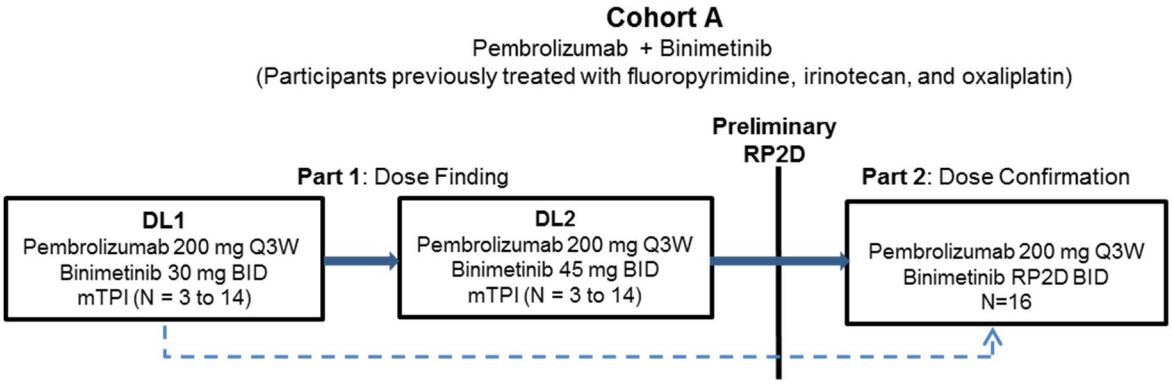
(Table 2). For example, if 1 out of 3 participants at a given dose level experiences a DLT, no more than an additional 3 participants may be enrolled at this dose level until additional DLT data are available since this dose would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4 out of 6 participants). New participants will be enrolled to the next dose level based on the decision as outlined in the mTPI design (see Table 2). There will be no intra-participant dose level escalation or dose level de-escalation for participants enrolled in this study (ie, 1 participant will be assigned to 1 dose level of the study drug). The definition of DLTs and the criteria for dose modification are outlined in Sections 5.1.3 and 7.2, respectively. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D. Based on the emerging safety and/or efficacy signals, an alternate dose level may be explored.

The totality of the data will be considered before deciding on the dose(s) to carry forward to Part 2.

Treatment allocation will be accomplished by non-random assignment. If a participant meets the eligibility criteria for Cohorts B and C (i.e., previously untreated) or Cohorts D and E (i.e., previously treated with one line of fluoropyrimidine-based therapy) then IVRS/IWRS will alternate assignments between the 2 cohorts with the same eligibility criteria. Treatment for each cohort in Part 2 will begin once a preliminary RP2D for that cohort is identified in Part 1.

5.1.1.2 Cohort A: Pembrolizumab plus Binimetinib (Participants Previously Treated with Fluoropyrimidine, Irinotecan, and Oxaliplatin)

The dose of pembrolizumab will remain constant at 200 mg Q3W (see Section 5.5.1.1.1). Two dose levels of binimetinib will be explored: 30 mg BID and 45 mg BID. The starting dose of binimetinib will be 30 mg BID and is described in Section 5.5.1.1.2. The dose level of binimetinib will be escalated to 45 mg BID, based upon the mTPI design rules, as outlined in Section 5.1.1.

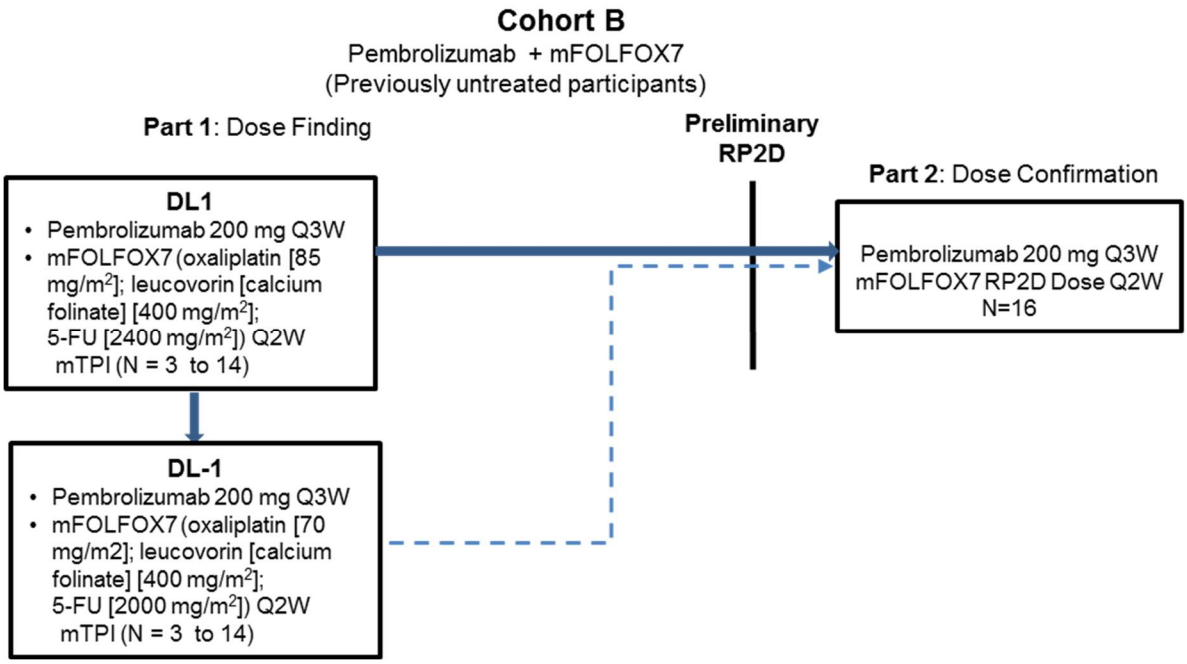


Abbreviations: DL = dose level; 5-FU = fluorouracil; mTPI = modified toxicity probability interval; RP2D = recommended Phase 2 dose; Q3W = every 3 weeks.

Figure 1 Study Diagram (Cohort A)

5.1.1.3 Cohort B: Pembrolizumab plus mFOLFOX7 (Previously Untreated Participants)

mFOLFOX7 in combination with pembrolizumab will be explored. The starting dose for mFOLFOX7 is the standard dose routinely used in clinical practice and is described in Section 5.5.1.1.3. There will be no dose escalation of the standard dose of mFOLFOX7. If the standard dose mFOLFOX7 is deemed too toxic per mTPI, the dose of mFOLFOX7 may be de-escalated per Figure 2, as outlined in Section 5.1.1. The dose of pembrolizumab will remain constant at 200 mg Q3W.

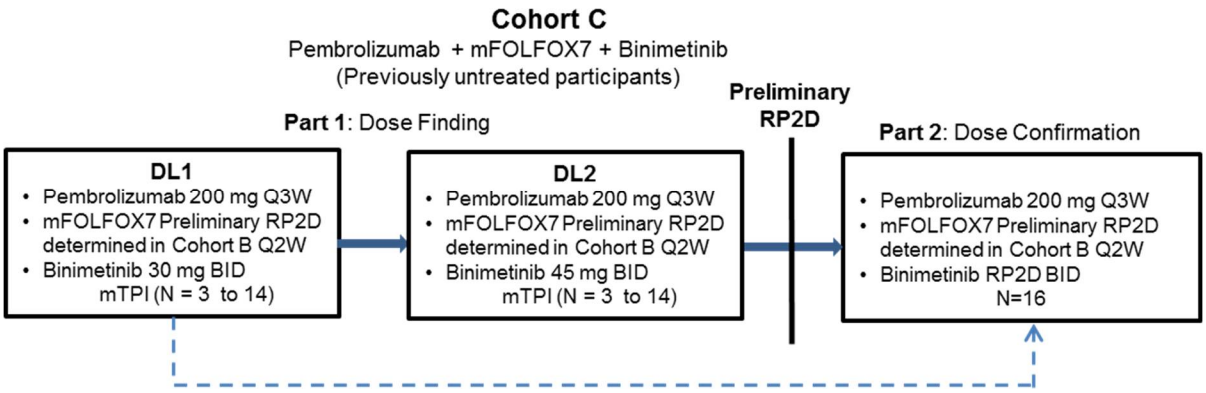


Abbreviations: BID = twice daily; DL = dose level; 5-FU = fluorouracil; mTPI = modified toxicity probability interval; RP2D = recommended Phase 2 dose; Q2W = every 2 weeks; Q3W = every 3 weeks.
Notes: DL1: standard dose. Please see Section 5.1.2 – Tolerability Evaluation Rules and Dose Finding.
DL-1: de-escalation dose

Figure 2 Study Diagram (Cohort B)

5.1.1.4 Cohort C: Pembrolizumab plus mFOLFOX7 plus Binimetinib (Previously Untreated Participants)

Participant may initiate enrollment in Cohort C after the preliminary RP2D decision has been made in Cohort B (pembrolizumab plus mFOLFOX7). Two dose levels of binimetinib (in combination with pembrolizumab and mFOLFOX7) will be explored. The starting dose of binimetinib will be 30 mg BID. The dose level of binimetinib will be escalated to 45 mg BID, based upon the occurrence of DLTs and the mTPI design rules as outlined in Section 5.1.1.

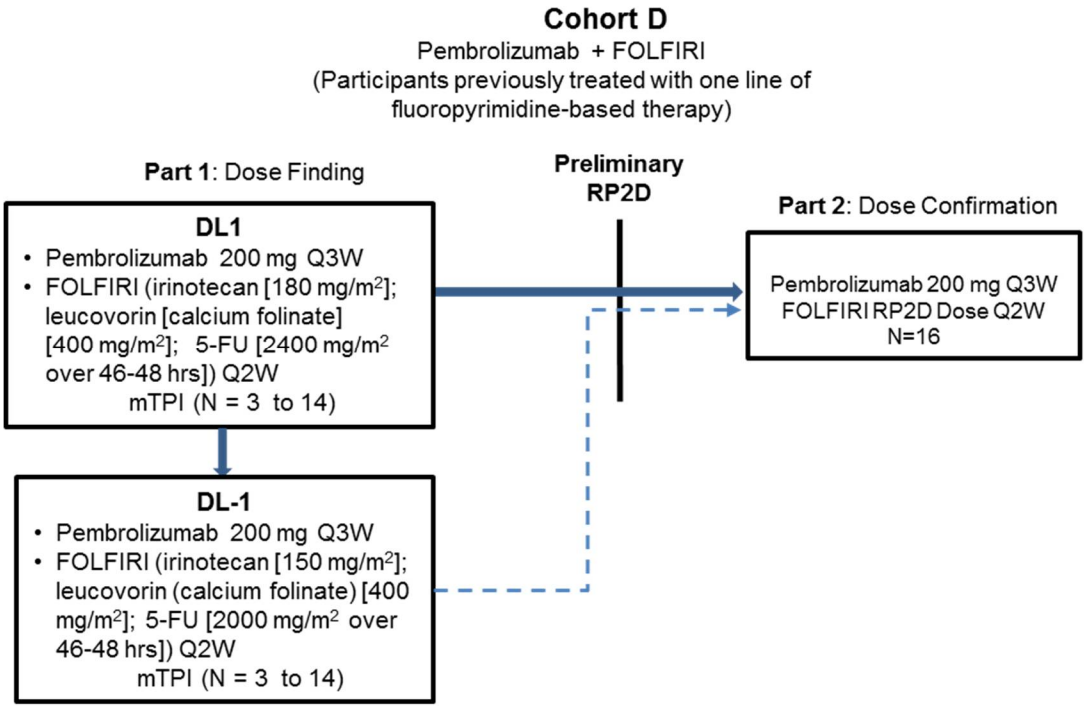


Abbreviations: BID = twice daily; DL = dose level; 5-FU = fluorouracil; mTPI = modified toxicity probability interval; RP2D = recommended Phase 2 dose; Q2W=every 2 weeks; Q3W=every 3 weeks.
Notes: DL1: standard dose. Please see Section 5.1.2 – Tolerability Evaluation Rules and Dose Finding.
DL2: escalation dose

Figure 3 Study Diagram (Cohort C)

5.1.1.5 Cohort D: Pembrolizumab plus FOLFIRI (Participants Previously Treated With One Line of Fluoropyrimidine plus Oxaliplatin-Based Therapy)

FOLFIRI in combination with pembrolizumab will be explored. The starting dose of pembrolizumab will remain constant at 200 mg Q3W. The starting standard dose for FOLFIRI is the dose routinely used in clinical practice and is described in Section 5.5.1.1.4. There will be no dose escalation of the standard dose of FOLFIRI. The dose level of FOLFIRI may be de-escalated per Figure 4 based upon occurrence of DLTs and the mTPI design rules as outlined in Section 5.1.1.

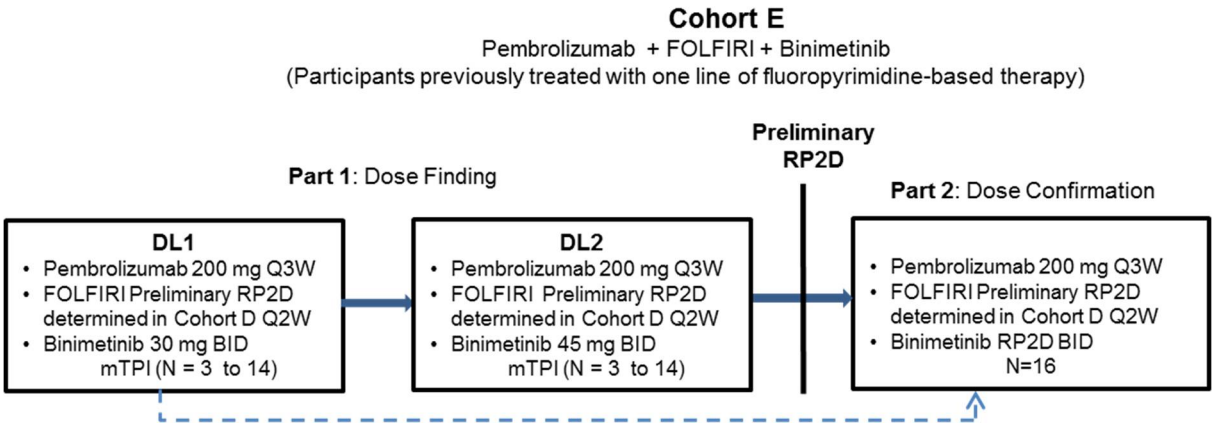


Abbreviations: BID = twice daily; DL = dose level; 5-FU = fluorouracil; mTPI = modified toxicity probability interval; RP2D = recommended Phase 2 dose; Q2W = every 2 weeks; Q3W = every 3 weeks.
Notes: DL1: standard dose. DL-1: de-escalation dose.

Figure 4 Study Diagram (Cohort D)

5.1.1.6 Cohort E: Pembrolizumab plus FOLFIRI plus Binimetinib (Participants Previously Treated With One Line of Fluoropyrimidine plus Oxiplatin-Based Therapy)

Participant may initiate enrollment in Cohort E after the preliminary RP2D decision has been made in Cohort D (pembrolizumab plus FOLFIRI). Two dose levels of binimetinib (in combination with pembrolizumab and FOLFIRI) will be explored. The starting dose of binimetinib will be 30 mg BID. The dose level of binimetinib will be escalated to 45 mg BID, based upon the occurrence of DLTs and the mTPI design rules as outlined in Section 5.1.1.



Abbreviations: BID = twice daily; DL = dose level; 5-FU = fluorouracil; mTPI = modified toxicity probability interval; RP2D = recommended Phase 2 dose; Q2W = every 2 weeks; Q3W = every 3 weeks.
Notes: DL1: standard dose. Please see Section 5.1.2 – Tolerability Evaluation Rules and Dose Finding.
DL2: escalation dose

Figure 5 Study Diagram (Cohort E)

5.1.1.7 Part 2 (Dose Confirmation)

Each cohort can proceed to Part 2 independently after a preliminary RP2D for that cohort is identified in Part 1. In Part 2, approximately 16 additional participants per cohort will be treated at the doses identified using the mTPI design in Part 1 to ensure at least 30 participants are treated at RP2D.

5.1.1.8 Part 1 and Part 2

Participants in both parts of the trial may receive up to 2 years of treatment with pembrolizumab (35 administrations) and binimetinib and treatment will continue until disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment. Treatment with SOC chemotherapy (mFOLFOX7 or FOLFIRI) will continue per Investigator's decision.

Participants will be monitored for the development of AEs, and for clinical and/or radiographic evidence of disease progression according to RECIST Version 1.1. However iRECIST could be used by the investigator for treatment decision. In participants who have initial evidence of radiological PD by RECIST Version 1.1, it will be at the discretion of the investigator whether or not to continue a participant on study treatment until repeat imaging is obtained to determine whether participant's disease is progressing or the initial evidence represents a 'pseudoprogression or tumor flare'. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may continue to receive study treatment until tumor assessment is repeated ≥4 weeks later in order to confirm PD by iRECIST per site assessment.

Time period and frequency for collecting AE, SAE and other reportable safety event information is outlined in Section 9.3.1.

Participants who discontinue treatment for reasons other than confirmed disease progression will have post-treatment follow-up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first.

After confirmed disease progression, each participant will be contacted (eg, by telephone) every 12 weeks for survival until withdrawal of consent to participate in the trial, becoming lost to follow-up, death, or end of the trial, whichever occurs first.

The trial will be conducted in conformance with GCP. Adverse events will be evaluated according to criteria outlined in the NCI CTCAE, Version 4.0 or later.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities - Section 2.0. Details of each procedure are provided in Section 9.0 – Study Assessments and Procedures.

5.1.2 Tolerability Evaluation Rules and Dose Finding

Two dose levels of binimetinib and the dose levels for SOC chemotherapies (mFOLFOX7 and FOLFIRI) are provided in Table 3. Dose escalation will continue as outlined above (Section 5.1.1) according to mTPI dose finding rules.

Table 3 Dose Levels in Cohorts A, B, C, D, and E (Parts 1 [Dose Finding] and 2 [Dose Confirmation])

		Regimen	
Cohort	**Dose Level**	**Part 1 (Dose Finding)**	**Part 2 (Dose Confirmation)**
Cohort A			
Pembrolizumab + Binimetinib	DL1	• Pembrolizumab 200 mg IV Q3W • Binimetinib 30 mg (oral) BID	• Pembrolizumab 200 mg IV Q3W + binimetinib (preliminary RP2D) (oral) BID
	DL2	• Pembrolizumab 200 mg IV Q3W • Binimetinib 45 mg (oral) BID	
Cohort B			
Pembrolizumab + mFOLFOX7	DL1	• Pembrolizumab 200 mg IV Q3W • mFOLFOX7 (oxaliplatin [85 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU [2400 mg/m^2 over 46-48 hrs]) IV Q2W	• Pembrolizumab 200 mg IV Q3W + mFOLFOX7 (preliminary RP2D) IV Q2W
	DL-1	• Pembrolizumab 200 mg IV Q3W • mFOLFOX7 (oxaliplatin [70 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU [2000 mg/m^2 over 46-48 hrs]) IV Q2W	
Cohort C			
Pembrolizumab + mFOLFOX7 + Binimetinib	DL1	• Pembrolizumab 200 mg IV Q3W • mFOLFOX7 (preliminary RP2D determined in Cohort B) IV Q2W • Binimetinib 30 mg (oral) BID	• Pembrolizumab 200 mg IV Q3W + mFOLFOX7 (preliminary RP2D determined in Cohort B) IV Q2W + binimetinib (preliminary RP2D) (oral) BID
	DL2	• Pembrolizumab 200 mg IV Q3W • mFOLFOX7 [preliminary RP2D determined in Cohort B] IV Q2W • Binimetinib 45 mg (oral) BID	
Cohort D			
Pembrolizumab + FOLFIRI	DL1	• Pembrolizumab 200 mg IV Q3W • FOLFIRI (irinotecan [180 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU [2400 mg/m^2 over 46-48 hrs]) IV Q2W	• Pembrolizumab 200 mg IV Q3W + FOLFIRI (preliminary RP2D) IV Q2W
	DL-1	• Pembrolizumab 200 mg IV Q3W • FOLFIRI (irinotecan [150 mg/m^2]; leucovorin (calcium folinate) [400 mg/m^2]; 5-FU [2000 mg/m^2 over 46-48 hrs]) IV Q2W	
Cohort E			
Pembrolizumab + FOLFIRI + Binimetinib	DL1	• Pembrolizumab 200 mg IV Q3W • FOLFIRI [preliminary RP2D determined in Cohort D] IV Q2W • Binimetinib 30 mg BID	• Pembrolizumab 200 mg IV Q3W + FOLFIRI (preliminary RP2D determined in Cohort D) IV Q2W + binimetinib (preliminary RP2D) BID
	DL2	• Pembrolizumab 200 mg IV Q3W • FOLFIRI [preliminary RP2D determined in Cohort D] IV Q2W • Binimetinib 45 mg (oral) BID	

Abbreviations: BID=twice daily; DL=dose level; DL1=standard dose; DL-1=de-escalation dose; DL2=escalation dose; 5-FU = fluorouracil; hrs = hours; Q2W = every 2 weeks; Q3W = every 3 weeks.

Individual participant dose interruptions and modifications may be implemented based on toxicity as described in Section 7.2.1. However, dose adjustments should not be made during the DLT observation period without discussion with the Sponsor.

The decision to enroll participants in the next dose level will be made by the sponsor in consultation with the participating investigators after reviewing the safety data.

Participants may continue on treatment until disease progression, unacceptable toxicity, investigator's decision to withdraw the participant, withdrawal of consent, development of an inter-current condition precluding further administration of study treatment, pregnancy of the participant, failure to comply with dosing evaluations or other study requirements, or administrative reasons.

5.1.3 Definition of Dose Limiting Toxicity

All toxicities will be graded using NCI CTCAE Version 4.0 based on the investigator assessment. The DLT window of observation will be during first **21-days** of treatment for Cohort A and first **28-days** of treatment for Cohorts B, C, D, and E to align with chemotherapy regimen.

The occurrence of any of the following toxicities will be considered a DLT, if assessed by the investigator to be possibly, probably or definitely related to study drug administration, excluding toxicities clearly not related to the drug, such as disease progression, environmental factors, unrelated trauma, etc.:

1. Grade 4 non-hematologic toxicity (not laboratory).
2. Grade 4 hematologic toxicity lasting >7 days.
3. Grade 3 thrombocytopenia associated with clinically significant bleeding.
4. Any non-hematologic AE Grade ≥3 in severity despite optimal supportive care should be considered a DLT, with the following exceptions:
   - Grade 3 fatigue lasting ≤3 days;
   - Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per SOC;
   - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per SOC.
5. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
   - Medical intervention is required to treat the participant, or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for >1 week.
6. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.

- Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

7. Any prolonged delay (>2 weeks) in initiating study therapy due to a treatment-related AE that started during the DLT period:
8. Any treatment-related toxicity that causes the participant to discontinue treatment during the DLT period.
9. Missing >25% of binimetinib doses as a result of drug-related AE(s) during the DLT period.
10. Grade 5 toxicity
11. Cardiac disorders
    - Absolute decrease in LVEF >10% compared with baseline and the LVEF is below the institution's lower limit of normal
    - Left ventricular systolic dysfunction Grade ≥3
    - Other cardiac disorders Grade ≥3
12. Vascular disorders
    - Hypertension CTCAE Grade ≥3 requiring more than 1 drug or more intensive therapy
    - Grade 4 hypertension
13. Eye disorders

    Retinal

    - Retinopathy or retinal detachment Grade ≥3, confirmed by ophthalmic examination
    - Retinal vein disorder including RVO, confirmed by ophthalmic examination

    Visual disturbances without ocular (retinal) changes

    - Blurred vision, flashing lights, floaters: Grade ≥3

    Other specify

    - Grade ≥3 for >21 consecutive days
    - Grade 4 confirmed by ophthalmic examination

If a participant experiences a DLT, trial treatment may be discontinued following discussion between the sponsor and Investigator. However, if the participant is deriving clinical benefit as determined by the Investigator from the trial treatment, the participant may be allowed to continue after discussion between the sponsor and the Investigator.

5.1.4 Replacement of Participants in DLT Period

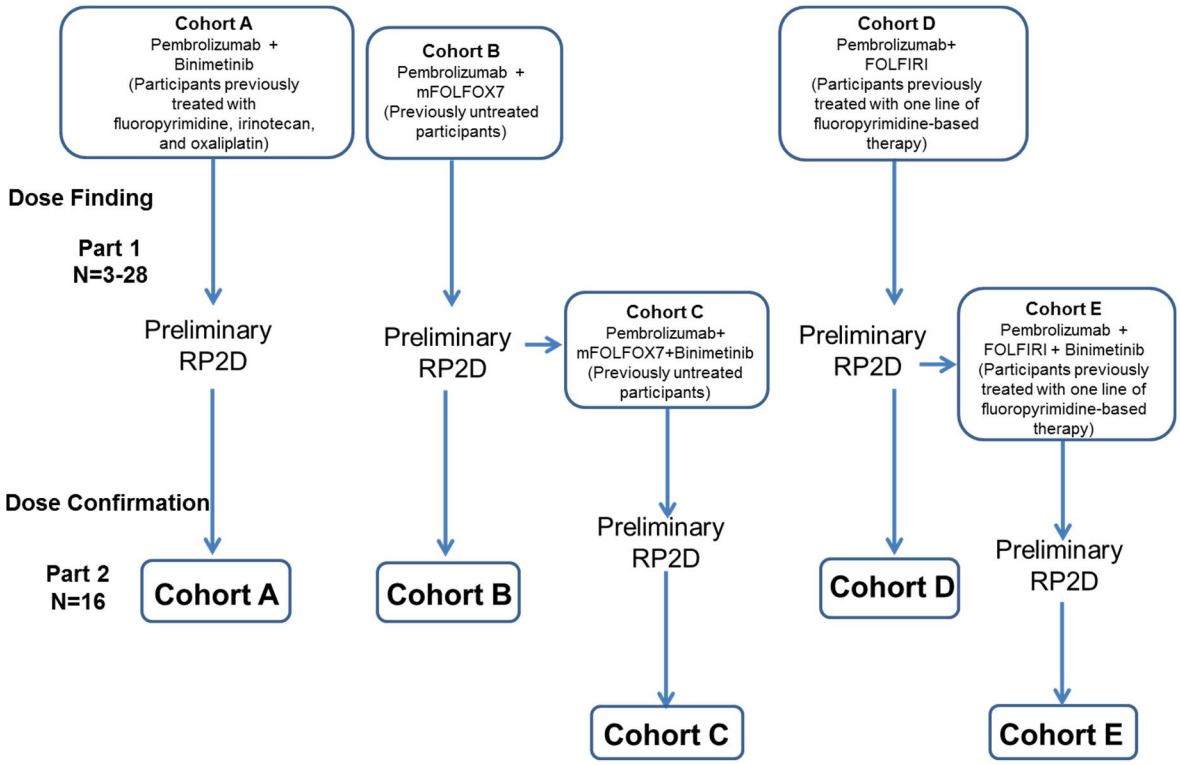
To fully evaluate the safety of the combination therapy in this study, all participants enrolled must meet the criteria for evaluability during the DLT period. Participants are considered non-evaluable and will be replaced if:

- They are enrolled but not treated,
- They discontinue from the trial prior to completing all safety evaluations due to reasons other than drug-related AEs,
- They received <90% of the total pembrolizumab infusion during the DLT period (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a drug-related event,
- They received <90% of the total SOC (mFOLFOX7 and FOLFIRI) infusion during the DLT period (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT,
- They received ≤75% of binimetinib doses intended for the trial during the DLT period and did not experience a drug-related event,
- They must take a prohibited concomitant medication during the DLT period, unless this medication is used to treat a study drug-related AE,
- They must undergo medical/surgical procedures or have logistical issues not related to study therapy (eg, elective surgery, unrelated medical events) during the DLT period.

Non-evaluable participants will not be counted toward the cohort total for DLT evaluation.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.5 Study Diagram



Abbreviations: n=number of participants; RP2D = recommended Phase 2 dose.

Figure 6 Study Diagram

5.2 Number of Participants

A maximum of approximately 220 participants will be enrolled (Parts 1 and 2). A target sample size of 159 participants will be used for trial planning purposes.

5.3 Beginning and End of Study Definition

The overall trial begins when the first participant signs the informed consent form (ICF). The overall trial ends when the last participant completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the participant is unable to be contacted by the investigator).

Once the participant has achieved the study objective or study has ended, the participant is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

5.3.1 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

A primary objective of this early Phase I trial is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve pharmacokinetic, pharmacodynamic and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s). If a finding (eg, pharmacokinetic, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical trial using the study treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial, results in the trial(s) or program being stopped for non-safety reasons, this also does not meet the definition of early trial termination.

Early trial termination is defined as a permanent discontinuation of the trial due to unanticipated concerns of safety to the trial participants arising from clinical or preclinical trials with the study treatment(s), comparator(s), drug(s) of the same class or methodology(ies) used in this trial.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

This trial will use ORR based on RECIST 1.1 as assessed by investigator as the secondary endpoint. RECIST 1.1 is a validated tool in assessing anti-cancer activity of an investigational agent.

Exploratory endpoints include DCR, DOR, and PFS as assessed by the investigator based on RECIST 1.1, ORR, DOR, DCR, and PFS as assessed by the investigator based on iRECIST as well as OS for each cohort.

A central imaging vendor will be used to collect, clean, and hold tumor imaging. Images will be collected for possible analysis by blinded, independent central review.

5.4.1.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs. Safety and tolerability will be assessed by clinical review throughout the trial. The toxicities and grades experienced by participants who have received study treatment, including AEs, SAEs and ECIs will be summarized. Other safety measures evaluated in study include laboratory tests, ECGs, ECHO/MUGA, vital signs, ECG measurements, physical examinations, and eye examination.

5.4.1.3 Pharmacokinetic Endpoints

Binimetinib was found to be a weak inhibitor of human liver microsomal UGT1A-mediated SN-38 conjugation, with an IC_{50} value greater than 25 μM. Irinotecan (pro-drug) is a substrate of extensive metabolic conversion by various enzyme systems, including carboxylesterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. The effects of binimetinib on the PK of irinotecan and SN-38, conversely, to estimate the effects of irinotecan and SN-38 on the PK of binimetinib will be explored. Blood samples of binimetinib, irinotecan and SN-38 will be obtained to measure PK of binimetinib, irinotecan, and SN-38.

5.4.1.4 Pharmacodynamic Endpoints

Not applicable.

5.4.1.5 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating participants. Thus, to aid future participants, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/PD biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules.

Investigations may include but are not limited to:

- Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing): This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. CCI [redacted] CCI
- Genetic (DNA) analyses from tumor: The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (eg, mutations, methylation status, MSI). Key molecular changes of interest to immune-oncology drug development include (for example) the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a "hyper-mutated" state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome.

- Pretreatment and posttreatment tumor (when obtained) and blood samples collected in this study may undergo proteomic, genomic and transcriptional analyses (both DNA and RNA analyses). Additional research may evaluate factors important for predicting responsiveness or resistance to binimetinib and pembrolizumab combination therapy and other immunologic targets. CCI [redacted] CCI [redacted]
- Tumor and blood RNA analyses: Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. CCI [redacted] CCI [redacted]
- Proteomics and IHC using blood or tumor: tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). CCI [redacted] CCI [redacted] CCI [redacted] Tumor tissue may, therefore, be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in participant selection for pembrolizumab therapy.
- Other blood derived biomarkers: In addition to expression on tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumors and released into the blood. Assays such as enzyme-linked immunoassay measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

5.4.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease

being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate). DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

5.4.1.6 Microsatellite Instability Testing

Mismatch repair proteins, or MSI loci testing for CRC is already clinically indicated as per NCCN [National Comprehensive Cancer Network 2017], ESMO [Van Cutsem, E., et al 2016], and ASCO guidelines [Sepulveda, A. R., et al 2017]. MMR or MSI status will be performed locally. Archived tumor samples or newly obtained biopsies will be used for determining MSI/MMR status by the site's local laboratory.

MMR or MSI status is determined by examining either 1) protein expression by IHC of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) or 2) 5 tumor microsatellite loci using PCR-based assay, respectively.

Tumors are classified as MSI-H when at least 2 allelic shifts among the 5 analyzed microsatellite markers are detected by PCR, or absence of at least 1 of 4 MMR proteins expression is detected by IHC (also called mismatch repair deficient, dMMR). Confirmation of non-MSI-H/pMMR status by one testing method (either PCR or IHC) is sufficient for eligibility. However, both methods should indicate pMMR and non-MSI-H status in participants who had both tests done. Sponsor consultation is required if further investigation led to confirmation of pMMR/non MSI-H status by the investigator.

5.4.1.7 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of Future Biomedical Research are presented in Appendix 7 – Collection and Management of Specimens for Future Biomedical Research.

5.4.2 Rationale for The Use of Comparator/Placebo

This study does not include comparators or placebo.

5.5 Justification for Dose

5.5.1 Starting Dose for This Trial

5.5.1.1 Justification for Treatment Regimen

5.5.1.1.1 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing

provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

5.5.1.1.2 Binimetinib Starting Dose

The starting dose of binimetinib will be 30 mg oral BID and the dose will be escalated to 45 mg oral BID per the mTPI rule. Rationale for these doses is based on studies conducted in patients with solid tumors. ARRAY-162-111 was a Phase I, open-label, dose-escalation study of oral binimetinib in patients with advanced solid tumors followed by expansion cohorts in patients with advanced or metastatic biliary cancer or KRAS- or BRAF-mutant mCRC. A total of 93 participants received at least 1 dose of binimetinib. Nineteen patients with advanced solid tumors received binimetinib in the dose-escalation phase. Four dose levels were evaluated: 30 mg BID, 45 mg BID, 60 mg BID and 80 mg BID. Two of the 4 participants receiving 80 mg BID experienced DLTs (Grade 3 chorioretinopathy and Grade 3 dermatitis acneiform despite maximal treatment measures), thus the 80 mg BID dose was declared non-tolerable. Seven participants were enrolled at 60 mg BID and no DLTs were observed, therefore, 60 mg BID was declared the MTD. Following completion of the Dose-escalation Phase, a total of 74 participants were enrolled in the Expansion Phase, 28 participants in the biliary cancer cohort, 31 participants in KRAS-mutant CRC cohort and 15 participants in the BRAF-mutant CRC cohort. After initiation of the Expansion Phase, a higher-than-expected frequency of ocular AEs affected the ability to treat participants continuously at the MTD, thus a reduced dose of 45 mg BID was implemented for the remainder of newly enrolled participants in the expansion phase cohorts.

Study CMEK162X1101 was an open-label, dose escalation, Phase I study of binimetinib as a single agent in Japanese participants with advanced solid tumors with the expansion part in participants whose tumors harbored RAS or BRAF mutations. Twenty-one participants were enrolled and treated with at least 1 dose of binimetinib (6 participants with 30 mg BID and 15 participants with 45 mg BID). Dose-limiting toxicities were reported during the dose escalation part for determination of the MTD. A total of 2 participants in the 45 mg BID dose level cohort reported 2 DLTs, both of which were recurrent Grade 2 detachment of retinal pigment epithelium. These events were judged as DLTs due to recurrence of the toxicity at the same grade while the dose of study drug was reduced. Therefore, 45 mg BID was declared the MTD in Japanese participants. No DLT was reported in participants enrolled in the expansion part.

In addition, a Phase I study evaluated binimetinib 30 mg BID and 45 mg BID dose in combination with mFOLFOX7 in heavily treated metastatic CRC patients (Section 5.5.1.1.2), and these 2 doses of binimetinib were well tolerated. Taken together, 30 mg BID and 45 BID doses are appropriate doses to be explored in the current trial [Thet Cho, M., et al 2016].

5.5.1.1.3 mFOLFOX7 Starting Dose

The starting dose of mFOLFOX7 (oxaliplatin 85 mg/m^2 IV infusion, leucovorin 400 mg/m^2 IV infusion, 5-FU 2400 mg/m^2 IV infusion over 46 to 48-hour infusion) Q2W, which is

considered a globally accepted SOC [National Comprehensive Cancer Network 2017] [Hochster, H. S., et al 2014].

5.5.1.1.4 FOLFIRI Starting Dose

The starting dose of FOLFIRI (irinotecan 180 mg/m^2 IV over 30-90 minutes, leucovorin 400 mg/m^2 IV infusion, 5-FU 2400 mg/m^2 IV over 46 to 48-hour infusion) Q2W, which is considered globally accepted SOC [National Comprehensive Cancer Network 2017].

5.5.2 Maximum Dose/Exposure for This Trial

The dose of pembrolizumab will be 200 mg administered intravenously Q3W and will remain constant.

The dose of pembrolizumab is based on single agent doses tested as well as the highest doses tested in combination in Phase I to II trials (See Section 5.5.1.1 and package insert for KEYTRUDA™).

The maximum dose of binimetinib for this trial will be 45 mg administered orally BID (maximum 90 mg total per day). The maximum dose of binimetinib is based on the single agent doses tested in participants with advanced solid tumors followed by expansion cohorts in participants with advanced or metastatic biliary cancer of KRAS-or BRAF-mutant mCRC in Study ARRAY-162 [Thet Cho, M., et al 2016] (See Section 5.5.1.1.2).

The maximum dose of mFOLFOX7 and FOLFIRI is the starting dose as outlined in Sections 5.5.1.1.3 and 5.5.1.1.4, respectively.

6. Study Population

Male and female participants with non-MSI-H/pMMR mCRC will be enrolled in this trial.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male and female participants who are at least 18 years of age on the day of signing consent will be eligible for enrollment in the study.
2. Have a histologically-confirmed, unresectable or metastatic (Stage IV American Joint Committee on Cancer seventh edition) CRC.
3. Have a locally determined non-MSI-H/pMMR tumor status (Section 5.4.1.6).
4. Have at least 1 radiologically measurable lesion as defined by RECIST 1.1.
5. Have an ECOG performance status of 0 or 1 prior to treatment initiation.
6. Have a life expectancy of at least 3 months.

7. Participants must have the ability to swallow and retain oral medication and not have any clinically significant gastrointestinal abnormalities that might alter absorption.
8. Have adequate organ function as defined in Table 4. All screening labs should be performed within 10 days prior to the first dose of trial treatment.

Table 4 Inclusion Criteria Laboratory Parameters

Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine OR Calculated* serum creatinine clearance (GFR can be used in place of creatine or creatinine clearance)	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for participants with creatinine levels >1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 X ULN or direct bilirubin ≤ULN for participants with total bilirubin >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN OR ≤5.0 X ULN for participants with liver metastases
Albumin	≥3.0 g/L
Coagulation	
International Normalized Ratio (INR) or prothrombin time (PT) or activated partial thromboplastin time (aPTT)	≤1.5X ULN unless participant is receiving anticoagulant therapy as long as the PT or aPTT is within the therapeutic range for the intended use of the anticoagulants
*Calculate serum creatinine clearance using the standard Cockcroft-Gault formula. Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; GFR= glomerular filtration rate; INR=International Normalized Ratio; SGOT=serum glutamic oxaloacetic transaminase; SGPT= serum glutamic-pyruvic transaminase; ULN = upper limit of normal.	

Participants for Cohort A

9. Must have been previously treated with fluoropyrimidine, irinotecan, and oxaliplatin.

   Note: Adjuvant chemotherapy counts as a first line of prior systemic therapy if there is documented disease progression within 12 months of chemotherapy completion.

Participants for Cohorts B and C

10. Must not have received prior systemic chemotherapy for Stage IV CRC.

    Note: Participants who have received adjuvant chemotherapy for non-Stage IV CRC and have documented disease progression within 12 months of chemotherapy completion will not be eligible as these participants may have relative resistance to the proposed 1L regimen, which may undermine the adequate efficacy assessment of this 1L combination.

Participants for Cohorts D and E

11. Must have been previously treated with 1 line of therapy including a fluoropyrimidine plus an oxaliplatin-based regimen.

    Note: Adjuvant chemotherapy counts as 1 line of prior systemic therapy if there is documented disease progression within 12 months of chemotherapy completion.

Participants for Cohorts A, C, and E

12. Participants must have a 12-lead ECG and ECHO or MUGA scan performed by the investigator or other qualified person to evaluate cardiac function prior to enrollment in the study. Adequate cardiac function will be assessed by:
    a) LVEF ≥50% as determined by MUGA scan or ECHO; and
    b) QT interval calculated according to the Fridericia method (QTcF) value ≤480 msec (mean of 3 measurements corrected for heart rate using Fridericia's formula).

Contraception

Male participants:

13. A male participant must agree to use a contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 180 days, after the last dose of study treatment and refrain from donating sperm during this period.
    a) Male participants with pregnant partners must agree to use a condom.
    b) No additional method of contraception is required for the pregnant partner.

Female participants:

14. A female participant is eligible to participate if she is not pregnant (see Appendix 6), not breastfeeding, and at least one of the following conditions applies:
    a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 6
    OR
    b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 during the treatment period and for at least 180 days after the last dose of study treatment.

Informed Consent

15. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial. The participant may also provide consent for Future Biomedical Research. However, the participant may participate in the main trial without participating in Future Biomedical Research.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Is currently participating and receiving study therapy in a study of an investigational agent or has participated and received study therapy in a study of an investigational agent or has used an investigational device within 28 days of administration of MK-3475.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.

2. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study therapy, or has not recovered to CTCAE Grade 1 or better from any adverse events that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual immune-related adverse events). Participants receiving ongoing replacement hormone therapy for endocrine immune-related adverse events will not be excluded from participation in this study.
3. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer, or other in-situ cancers.
4. Has clinically active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by MRI of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks prior to first study treatment administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks prior to enrollment.
5. Has a known hypersensitivity, intolerability or contraindication to any component of study treatment (eg, known deficiency of the enzyme DPD), including premedication.
6. Has any active infection requiring systemic therapy.
7. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
8. Has received prior therapy with compounds targeting PD-1, PD-L1, PD-L2, or a MAPK pathway inhibitor (eg, BRAF, MEK, ERK inhibitors).
9. Has an autoimmune disease that has required systemic treatment in the past 2 years with use of disease modifying agents, corticosteroids, or immunosuppressive drugs. Replacement therapy (eg, thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.
11. Has known history of HIV infection. No HIV testing is required unless mandated by local health authority.

12. Has a known history of Hepatitis B (defined as HB_SAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note**:** No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

13. Has received live vaccine within 30 days of the planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.

14. Has undergone major surgery and has not recovered adequately from any toxicity and/or complications from the intervention prior to starting study therapy.

15. Has baseline peripheral neuropathy/paresthesia
    a. Grade >1 for potential participants for Cohort A, D or E in Part 1
    b. Grade >0 for potential participants for Cohort B or C in Part 1 (oxaliplatin containing cohorts)
    c. Grade >2 for potential participants for Cohort A, D or E in Part 2
    d. Grade >1 for potential participants for Cohort B or C in Part 2 (oxaliplatin containing cohorts)

16. Have any medical, psychiatric, cognitive, or other conditions that may compromise the participant's ability to understand the participant information, give informed consent, comply with the study protocol, or complete the study.

17. Has symptomatic CHF (i.e. Grade 2 or higher), history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality ≤6 months prior to start of study treatment, except atrial fibrillation and PSVT.

18. Have a history of acute or chronic pancreatitis.

19. Have existing uncontrolled arterial hypertension (SBP ≥150 mm Hg or DBP ≥100 mm Hg) despite appropriate medical therapy.

20. Have a history of thromboembolic or cerebrovascular events within 6 months prior to registration, including TIAs, CVAs, deep vein thrombosis, or pulmonary embolism.

21. Have neuromuscular disorders associated with an elevated creatine kinase (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy.

Potential Participants for Cohorts A, C or E who are to Receive Binimetinib:

22. Have a history of, or current, RVO or current risk factors for RVO (eg, uncontrolled glaucoma, ocular hypertension, history of hyperviscosity, or hypercoagulability syndromes).

23. Have retinal degenerative disease.

Potential Participants for Cohorts A, C, D or E:

24. Have a known history of Gilbert's Syndrome.

Potential Participants for Cohorts D or E:

25. Has a previous treatment with irinotecan will be excluded.
26. Has plans to use, or is using, any herbal medications/supplements or any medications or foods that are strong inhibitors or inducers of cytochrome P450 3A 4/5 ≤1 week prior to the start of study treatment.

Pregnancy Exclusion

27. A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study treatment (see Appendix 6). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

6.3 Lifestyle Restrictions

Participants receiving 5-FU (mFOLFOX7 or FOLFIRI) must avoid exposure to sunlight due drug-induced photosensitivity.

6.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modification is required to manage AEs such as diarrhea, nausea, or vomiting.

6.3.2 Caffeine, Alcohol, and Tobacco

There are no study specific restrictions regarding caffeine, alcohol, and tobacco.

6.3.3 Activity

There are no study specific restrictions.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

If a participant withdraws from the trial, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same treatment or treatment sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment number. The trial site should contact the Sponsor for the replacement participant's treatment number.

Please see Section 5.1.4 regarding replacement of participants during the DLT period.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatment(s) to be used in this trial are outlined below in Table 5.

Table 5 Study Treatment(s)

Study Treatment Name		Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
Pembrolizumab (MK-3475)		Solution for Infusion	100 mg/4 mL	200 mg Q3W	IV infusion	Provided centrally by the Sponsor
Binimetinib		Tablet	15 mg	30 mg BID 45 mg BID	Oral	Provided centrally by the Sponsor
mFOLFOX7	Oxaliplatin	Solution for Infusion	5 mg/mL	85 mg/m^2 Q2W 70 mg/m^2 Q2W	IV infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
	Leucovorin (Calcium Folinate)	Solution for Injection	10 mg/mL	400 mg/m^2 Q2W		
	5-FU	Solution for Injection	50 mg/mL	2400 mg/m^2 Q2W 2000 mg/m^2 Q2W		
FOLFIRI	Irinotecan	Solution for Infusion	20 mg/mL	180 mg/m^2 Q2W 150 mg/m^2 Q2W	IV infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
	Leucovorin (Calcium Folinate)	Solution for Injection	10 mg/mL	400 mg/m^2 Q2W		
	5-FU	Solution for Injection	50 mg/mL	2400 mg/m^2 Q2W 2000 mg/m^2 Q2W		

Abbreviations: BID=twice daily; FOLFIRI = (irinotecan [180 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2); mFOLFOX7 = (oxaliplatin [85 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2); 5-FU=Fluorouracil; IV=intravenous; Q2W= every 2 weeks; Q3W=every 3 weeks.

All supplies indicated in Table 5 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

7.2 Dose Modification (Escalation/Titration/Other)

7.2.1 Guideline for Dose Modification

Guidelines for dose delay and dose modification are described below and are applicable to the start of each cycle as well as during the cycle if treatment-related toxicities occur. If treatment-related toxicities occur that require supportive care including steroid use follow the general recommendations in Section 7.7.1 - Rescue Medications & Supportive Care.

Dosing interruptions are permitted after Cycle 1 in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, participant vacation, and/or holidays). Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

7.2.1.1 Dose Modification Due to Adverse Events

The CTCAE Version 4.0 must be used to grade the severity of adverse events. The Investigator may attribute each toxicity event to pembrolizumab alone, binimetinib alone, or to any of the components of the standard of care chemotherapies (mFOLFOX7 and FOLFIRI), or to any component of the combination therapy, and follow corresponding dose modification guidelines described in Section 7.2.1.2 to Section 7.2.1.5.

If a participant experiences overlapping toxicities that may be attributed to the combination regimen as a whole rather than to a single drug, Investigators should consider dose reduction/interruption/discontinuation of all the drugs in the combination, in addition to considering the discontinuation of the drug that most likely causes the toxicities, and/or consult with the Sponsor. Early recognition of immune related adverse effect and initiation of systemic corticosteroids is critical to reduce the risk of complications. Investigators should follow individual guidelines described in Table 6 (pembrolizumab), Table 7 (binimetinib), Section 7.2.1.4 (mFOLFOX7), or Section 7.2.1.5 (FOLFIRI), respectively, and/or consult with the Sponsor, to determine whether and when to resume the withheld/interrupted drug(s).

All AEs should be followed as clinically appropriate until stabilization or resolution.

The drug to which the investigator is attributing to the AE must be documented (AE eCRF, patient notes, etc.).

Exceptional circumstances to following the dose modification tables below should be consulted with the Sponsor.

7.2.1.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

See Section 7.7.1.4 for supportive care guidelines, including the use of corticosteroids.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

7.2.1.3 Binimetinib

The starting dose level for binimetinib is 30 mg BID, and a dose reduction below 30 mg BID is not allowed. Participants requiring additional reductions must discontinue binimetinib treatment. Dose interruptions of more than 21 days are not allowed. In the cases of the dose interruption of longer than 21 days due to an AE, discontinuation of binimetinib should be considered.

For participants who do not tolerate the 45 mg BID dosing schedule, dose adjustment to 30 mg BID is permitted in order to allow the participant to continue on study drug.

Missed/skipped doses will not be made up (ie, the participant should not double their dose if the previous dose was missed). When the toxicity that resulted in a dose reduction improves to and remains stable at Grade 1 or less for a minimum of 21 days, the dose can be re-escalated at the investigators discretion provided there are no other concomitant toxicities.

No dose re-escalation of binimetinib is allowed after dose reduction due to left ventricular dysfunction or prolonged QTcF ≥501 msec.

No dose re-escalation of binimetinib is allowed after a dose reduction due to retinal toxicity ≥ Grade 2.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. In general, doses should not be reduced or interrupted for Grade 1 toxicities, but treatment to control symptoms should be provided as appropriate.

Please refer to Table 7 for dose adjustment recommendations for binimetinib-induced toxicities.

Table 7 Dose Modification Guideline for Binimetinib

Toxicity	Dose Adjustment for Binimetinib
Eye disorders- Retinal Events (including serous detachment of the retina)	
Grade 1	Maintain dose level of binimetinib and repeat ophthalmic monitoring including visual acuity assessment and ocular coherence tomography (OCT) within 10 days.
Grade 2	Interrupt binimetinib dosing and refer the participant to ophthalmologist within 1 week and obtain OCT within 10 days: • If resolved to baseline or Grade ≤ 1 within 10 days, resume treatment at current dose level and continue schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 1 within 10 days, resume treatment at reduced dose level and continue the schedule of events of visual assessments established per protocol.
Grade 3	Interrupt binimetinib and refer the participant to ophthalmologist within 1 week and obtain OCT: • If resolved to baseline or Grade ≤ 2 within 7 days, resume treatment at current dose level and continue schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 2 within 7 days, continue to hold the binimetinib dose and repeat ophthalmic assessment in 10 days. o If resolved to baseline or Grade ≤ 2, resume treatment at reduced dose level and continue schedule of visual assessments established per protocol. o If remains Grade 3, permanently discontinue binimetinib.
Grade 4	Permanently discontinue binimetinib and immediately follow up with ophthalmic monitoring.
Eye disorder - RVO	
Any Grade	Permanently discontinue binimetinib.
Other eye disorders (i.e. Non-retinal Events)	
Grade 1-2	Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least 14 days until stabilization or resolution.
Grade 3	Interrupt binimetinib and refer participant to ophthalmologist within 1 week: • If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level of binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue binimetinib.
Grade 4	Permanently discontinue binimetinib.

Toxicity	Dose Adjustment for Binimetinib
Liver-related adverse events	
Grade 1 AST or ALT (> ULN - 3 x ULN)	Maintain dose level of binimetinib.
Grade 2 AST or ALT (> 3 - 5.0 x ULN or 3 x baseline value) AND blood bilirubin ≤ 2.0 x ULN	Interrupt dose of binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, maintain dose level of binimetinib. • If resolved in > 14 days, reduce dose level of binimetinib. Recurrence: • Interrupt dosing of binimetinib until resolved to Grade ≤1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at a reduced dose.
Grade 2 AST or ALT (> 3 - 5.0 x ULN or 3 x baseline value) AND blood bilirubin > 2.0 x ULN	Interrupt dose of binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 7 days, resume treatment at a reduced dose of binimetinib. • If not resolved in ≤ 7 days, permanently discontinue binimetinib.
Grade 3 AST or ALT (> 5.0 - 8.0 x ULN) AND blood bilirubin ≤ 2.0 x ULN	Interrupt dose of binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, maintain dose level of binimetinib. • If resolved in > 14 days, reduce dose level of binimetinib. Recurrence: • Interrupt dosing of binimetinib until resolved to Grade ≤1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at a reduced dose.
AST or ALT (>8 x ULN) AND blood bilirubin* ≤ 2.0 x ULN	Permanently discontinue binimetinib.
AST or ALT (> 5.0 x ULN) AND blood bilirubin* > 2.0 x ULN	Permanently discontinue binimetinib.
AST or ALT Grade 4 (> 20.0 x ULN)	Permanently discontinue binimetinib.

Toxicity	Dose Adjustment for Binimetinib
Cardiac disorders	
Left ventricular systolic dysfunction Asymptomatic decrease of >10% in LVEF compared to baseline and the LVEF is below the institution's lower limit of normal	Interrupt dose of binimetinib and repeat evaluation of LVEF within 2 weeks. • If the LVEF recovers (defined as LVEF ≥ 50% or ≥ LLN and absolute decrease ≤ 10% compared to baseline) ≤ 3 weeks, reduce 1 dose level after approval of the Sponsor Medical Monitor. Monitor LVEF 2 weeks after restarting on binimetinib, every 4 weeks for 12 weeks and subsequently as per protocol. • If the LVEF does not recover within 3 weeks, permanently discontinue participant from study treatment. Closely monitor LVEF until resolution (or 16 weeks).
Grade 3-4	Permanently discontinue participant from binimetinib. Closely monitor LVEF until resolution (or 16 weeks).
CK elevation	
Grade 1-2	Continue treatment on same dose level. Ensure patient is adequately hydrated. Monitor closely CK and serum creatinine levels. (If total CK ≥ 3 X ULN, measure isoenzymes and myoglobin in blood and urine).
Grade 3 (> 5.0 - 10.0 x ULN) without renal impairment (ie, serum creatinine < 1.5 x ULN or 1.5 x baseline)	If asymptomatic, maintain dose of binimetinib. Monitor closely and measure isoenzymes and myoglobin in blood and urine. If symptomatic (muscle pain/spasms or muscle weakness), interrupt dose of binimetinib until resolved to CTCAE Grade ≤ 1 and monitor closely, then: • If resolved in ≤ 21 days, reduce 1 dose level of binimetinib. • If resolved in > 21 days, permanently discontinue binimetinib.
Grade 4 without renal impairment (ie, serum creatinine < 1.5 x ULN or 1.5 x baseline)	If asymptomatic, interrupt dose of binimetinib and monitor closely. Ensure patient is adequately hydrated and monitor and measure isoenzymes and myoglobin in blood or urine, and serum creatinine. • If resolved in ≤ 21 days, reduce 1 dose level of binimetinib. • If resolved in > 21 days, permanently discontinue binimetinib. If symptomatic, permanently discontinue binimetinib. If symptomatic (muscle pain/spasms), permanently discontinue binimetinib.
Grade 3 or 4 with renal impairment (ie, serum creatinine ≥ 1.5 x ULN or 1.5 x baseline)	Interrupt binimetinib dose until resolved to Grade < 1 or baseline level. Ensure patient is adequately hydrated. Monitor isoenzymes and myoglobin in blood or urine, and serum creatinine, then: • If resolved in ≤ 21 days, reduce 1 dose level of binimetinib. • If resolved in > 21 days, permanently discontinue binimetinib. Recurrence: • Permanently discontinue binimetinib

Toxicity	Dose Adjustment for Binimetinib
Rash	
Grade 1	Treatment with binimetinib should be maintained at the current dose. Initiate prophylactic regimen if it was not already and monitor closely.
Grade 2	First occurrence: Treatment with binimetinib should be maintained at the current dose and rash should be closely monitored. Initiate prophylactic regimen if it was not already started. Reassess within a maximum of 2 weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤ 1. Resume treatment at the same dose level. Second occurrence: Reassess within a maximum of 2 weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤ 1. Resume treatment at a reduced dose level. Only one dose reduction is permitted.
Grade 3	First occurrence: Treatment with binimetinib should be interrupted. Reassess the participant weekly. Consider referral to dermatologist and manage rash per dermatologist's recommendation. Interrupt treatment until improvement to Grade ≤ 1. Resume treatment with binimetinib at the same dose level. Second occurrence: Interrupt treatment until improvement to Grade ≤ 1. Resume treatment with binimetinib at a reduced dose level. If participant is at the lowest dose, participant should be discontinued. Consider referral to dermatologist and manage rash per dermatologist's recommendation.
Grade 4	Permanently discontinue binimetinib.
Diarrhea	
Uncomplicated Grade 1-2	Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Treatment with binimetinib may then be resumed at the same dose level.
Complicated Grade 1-2	Temporarily interrupt binimetinib treatment until resolved to Grade ≤ 1. Restart binimetinib at one reduced dose level. If participant is at the lowest dose, participant should be discontinued.
Grade 3-4	Temporarily interrupt binimetinib treatment until resolved to Grade ≤ 1. Restart binimetinib at a reduced dose level. If participant is at the lowest dose, participant should be discontinued.
Nausea/Vomiting	
Grade 1-2	Treatment with binimetinib should be maintained at the current dose. Promptly institute antiemetic measure.
Grade 3	Temporarily interrupt binimetinib treatment until resolved to Grade ≤ 1. Resume treatment with binimetinib at the same dose if, in the judgment of the investigator, the toxicity is considered to be unrelated to binimetinib, or at one reduced dose level. Note: Interrupt dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue binimetinib treatment

Toxicity	Dose Adjustment for Binimetinib
Interstitial lung disease/pneumonitis	
Grade 1	Maintain dose level of binimetinib. Monitor weekly.
Grade 2	Withhold binimetinib for up to 3 weeks. If improved to Grade 0 or 1, resume treatment at 1 reduced dose level of binimetinib. If not resolved within 3 weeks, permanently discontinue binimetinib.
Grade 3-4	Permanently discontinue binimetinib.
Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold binimetinib for up to 3 weeks. • If improved to Grade 0 or 1, resume at reduced dose. If not improved, permanently discontinue.
Life threatening PE	Permanently discontinue binimetinib.
All other adverse events (suspected to be related)	
Grade 1-2	If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider study drug interruption or reduction.
Grade 3	For other AEs, interrupt study drug until resolution to Grade ≤1 or to pre-treatment/baseline level. If the event resolves within 21 days then study drug may be restarted at a lower dose (one level below that previously received) based upon the Investigator's discretion.
Grade 4	Permanently discontinue study drug.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID= twice daily; CK=creatine kinase; CTC=Common Terminology Criteria; ECG=electrocardiogram; LLN= lower limit of normal; LVEF=left ventricular ejection fraction; OCT= ocular coherence tomography; RVO=retinal vein occlusion; QTc=Q-T interval QTcF=QT interval calculated according to the Fridericia method; ULN= upper limit of normal.

7.2.1.4 mFOLFOX7

Dose delays and treatment restarts will be made at the discretion of the site investigator according to institutional guidelines or local standard practice. The recommended dose reduction is stepwise by 20%. Discontinuation of treatment should be considered if dose reduction below the following dosage is required: Oxaliplatin 50 mg/m^2 and 5-FU infusion 1600 mg/m^2 46 to 48 hours.

7.2.1.5 FOLFIRI

Dose delays and treatment restarts will be made at the discretion of the site investigator according to institutional guidelines or local standard practice. The recommended dose reduction is stepwise by 20%. Discontinuation of treatment should be considered if dose reduction below the following dosage is required: Irinotecan 120 mg/m^2 and 5-FU infusion 1600 mg/m^2 46 to 48 hours.

7.3 Method of Treatment Assignment

Treatment allocation will be accomplished by non-random assignment. There are 5 planned treatment cohorts in Part 1 (dose finding) and Part 2 (dose confirmation). This is an open-

label trial. Treatment allocation will be accomplished by non-random assignment. If a participant meets the eligibility criteria for Cohorts B and C (ie, previously untreated) or Cohorts D and E (ie, previously treated with one line of fluoropyrimidine-based therapy), then IVRS/IWRS will alternate assignments between the 2 cohorts with the same eligibility criteria. Treatment for each cohort in Part 2 will begin once a preliminary RP2D for that cohort is identified in Part 1.

7.3.1 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

7.4 Blinding

This is an open-label trial; therefore, the Sponsor, investigator and participant will know the study drug administered.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The rationale for selection of doses to be used in this trial is provided in Section 3.2 – Background.

7.5.1.1 Pembrolizumab

The Pharmacy Manual contains specific instructions for preparation of the pembrolizumab infusion fluid and administration.

7.5.1.2 Binimetinib

Binimetinib is an oral medication, and it is supplied as film-coated tablets in dosage strength of 15 mg. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

7.5.1.3 Standard of Care Chemotherapies (mFOLFOX7 and FOLFIRI)

Preparation of SOC chemotherapies must follow local standards.

7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

Pembrolizumab and SOC chemotherapies will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Participants receiving binimetinib should be instructed to bring their study drug supply and bottles, to the site at each study visit. Compliance will be evaluated at each visit by review of an accounting of returned study drug.

Interruptions from the protocol specified treatment plan for ≥12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.7 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days of the first dose of study treatment, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (ie, after randomization or treatment allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the trial if both the Sponsor and the investigator agree.

Listed below are specific restrictions for concomitant therapy during the course of the trial: Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases (including retreatment for post- CR relapse) of this trial: Participants who, in the assessment of the investigator, require the use of any of the treatments mention for

clinical management should be discontinued from treatment. Participants may receive other medications that the investigator deems to be medically necessary.

- Antineoplastic systemic chemotherapy or biological therapy not specified in this study
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and binimetinib
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Glucocorticoids (inhaled steroids as part of a stable regimen for the treatment of asthma/ COPD are permitted) for any purpose other than to modulate symptoms from an AE. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Additionally, a short limited course of steroids may be used to treat medical conditions and/or AEs during the study after sponsor notification and consultation.

  Note: Use of prophylactic corticosteroids to avoid allergic reactions (eg, IV contrast dye) and as a part of anti-emetic therapy for chemotherapy is permitted.
- Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and ECIs as defined in Section 9.3.7.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

7.7.1 Rescue Medications & Supportive Care

For adverse events included in the protocol, if the investigator cannot definitively attribute to any particular component of the regimen, supportive care including steroid use should follow general recommendations below.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2 and Table 6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 8 in Section 7.7.1.1 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

7.7.1.1 Supportive Care Guidelines for Pembrolizumab

Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further treatment with pembrolizumab**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further treatment with pembrolizumab.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = oral.		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

7.7.1.2 Supportive Care Guidelines for Binimetinib

Hypertension

It is recommended that additional blood pressure monitoring occur for participants who may be at risk (participants with hypertension at baseline) or those with antecedents of hypertension or those treated with antihypertensive medication. Early initiation of treatment is recommended after diagnosis, with aggressive management of emergent hypertension.

Nausea and/or vomiting

Because nausea and vomiting have been reported for binimetinib, it is recommended that participants are educated on the possibility of occurrence of these side effects prior to starting study treatment. Participant education as well as proper management of nausea and/or vomiting at the first sign is important. Clinical judgment and experience of the treating physician should guide the management plan of each participant. Participants experiencing nausea and/or vomiting CTCAE Grade ≥1 should receive antiemetics at the discretion of the treating physician (as per local guideline). It is recommended that participants be provided a prescription for antiemetics, and are instructed on the use of antiemetics on the first day of study drug treatment. Prophylactic antiemetics such as dexamethasone 8 mg, prochlorperazine, or metoclopramide may be administered to participants on an "as needed" basis.

Dose interruption/reduction decisions for nausea and/or vomiting should be based on the CTCAE grade of the toxicity and the guidelines provided in Section 7.2.1.

As guidance for recommendations on supportive measures for the prevention and/or management of nausea and/or vomiting, the published recommendation from ASCO [Sepulveda, A. R., et al 2017], ESMO [Van Cutsem, E., et al 2016], and MASCC can be used [Basch, E., et al 2011] [Roila, F., et al 2010].

Diarrhea

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, participant education as outlined above as well as proper management of diarrhea is important.

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications section of the participant record. It is recommended that participants be provided loperamide tablets and are instructed on the use of loperamide on the first day of binimetinib treatment. In addition to the binimetinib-induced diarrhea dosing guidelines, these instructions should be provided at each visit and the site should ensure that the participant understands the instructions.

Explain the frequency of diarrhea and its relationship to NCI CTCAE grading.

Rule out other or concomitant causes which may include:

- Infection with *Candida*, *Salmonella*, *Clostridium difficile*, *Campylobacter*, *Giardia*, *Entamoeba* and *Cryptosporidium species* can lead to severe infections in immunosuppressed participants
- Medication-induced diarrhea
- Malabsorption/lactose intolerance
- Fecal impaction, partial bowel obstruction

For uncomplicated Grade 1/2 diarrhea

- Stop all lactose-containing products, alcohol and eat frequent small meals that include bananas, rice, applesauce, or toast)
- Stop laxatives, bulk fiber (ie, Metamucil®) and stool softeners (eg, docusate sodium; Colace®)
- Stop high-osmolar food supplements such as Ensure® Plus and Jevity® Plus (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (eg, water, Pedialyte®, Gatorade® or broth)
- Consider administration of standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool
- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval
- If uncomplicated Grade 1 to 2 diarrhea persists for more than 24 hours, escalate to high dose loperamide: 2 mg every 2 hours (max. of 16 mg/day) or after each unformed stool.

Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to 2 diarrhea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a 2L agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide).

For complicated Grade 1/2 diarrhea or any Grade 3 to 4 diarrhea

- The participant must call the investigator immediately
- If loperamide has not been initiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Administer IV fluids and electrolytes as needed. In case of severe dehydration, replace loperamide by octreotide.
- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the participant is diarrhea free for at least 24 hours.
- Hospitalization may need to be considered.

Note: (see Section 7.2.1.2 for pembrolizumab dose modification)

Skin Toxicity

Clinical judgment and experience of the treating physician should guide the management plan of each participant. In general, the following interventions are in addition to the rash dosing adjustment guidelines in Table 7:

- Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with study drug or later as needed.
- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back.

Topical agents include non-oily sunscreen (PABA free, SPF ≥ 30, UVA/UVB protection), topical steroids (preferably mometasone cream ie, Elocon®) and topical erythromycin (ie, Eryaknen® or topical pimecrolimus).

Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to the first dose, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2-3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild rash (CTCAE Grade 1)

- Consider prophylactic rash treatment if not already started.
- Topical or other topical corticosteroid (ie, mometasone cream) and/or topical antibiotic (ie, erythromycin 2%) are recommended.
- The participant should be reassessed within a maximum of 2 weeks or as per investigator opinion.

Moderate rash (CTCAE Grade 2)

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as: lymecycline (408 mg QD], doxycycline (100 mg BID) or minocycline (50 to 100 mg QD).
- Although there has been no evidence of phototoxicity or photosensitivity in participants being treated with binimetinib, doxycycline (or minocycline as 2L) should be used with thorough UV protection (ie, avoidance of direct exposure to sunlight, use of sunscreen and sunglasses).
- Use of acitretin is not recommended

Severe rash (CTCAE Grade 3-4)

CTCAE Grade 3

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, ie, 0.3 to 0.5 mg/kg) [Lacouture, M. E., et al 2011].
- Use of acitretin is not recommended.

CTCAE Grade 4

- Immediately discontinue the participant from study drug and treat the participant with oral and topical medications (see recommendation CTCAE Grade 3).

Symptomatic Treatment:

- It is strongly recommended that participants who develop rash/skin toxicities receive symptomatic treatment:
  - For pruritic lesions, use cool compresses and oral antihistaminic agents
  - For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics such as Fucicort®
  - For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)
  - For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgeon
  - For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

7.7.1.3 Supportive Care Guidelines for mFOLFOX7

Please refer to local guidelines and the label regarding supportive care for participants treated with SOC chemotherapies.

7.7.1.4 Supportive Care Guidelines for FOLFIRI

Participants should receive appropriate supportive care measures as deemed necessary by the site investigator including but not limited to the items outlined below:

Early Diarrhea:

- Occurring during or shortly after infusion of irinotecan is usually transient and infrequently severe. Early diarrhea may be prevented or treated. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of IV or subcutaneous atropine (unless clinically contraindicated).

Late Diarrhea:

- Occurring more than 24 hours after administration of irinotecan. Use loperamide 4 mg at the onset of diarrhea, then 2 mg every 2 hours until the participant is diarrhea-free for at least 12 hours.

Colitis/Ileus:

- Participants experiencing ileus should receive prompt antibiotic support.

7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.9 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - SoA and Section 9.10.3 – Discontinued Participants Continuing to be Monitored in the Study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant has a confirmed positive serum pregnancy test
- The participant is non-compliant with study treatment or procedures
- The participant has confirmed radiographic disease progression with the exception of the Sponsor approving treatment continuation as outlined in Section 9.2 - Efficacy Assessments

- The participant experiences unacceptable AEs as described in Section 9.3 - Adverse Events, Serious Adverse Events and Other Reportable Safety Events
- The participant develops an intercurrent illness other than another malignancy that prevents further administration of treatment
- The investigator decides to withdraw the participant
- The participant experiences recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed CR by local investigator assessments and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of binimetinib beyond the date when the initial CR was declared. SOC chemotherapies may continue administered at the discretion of the investigator.
- Noncompliance with study treatment or procedure requirements
- The participant experiences progression or recurrence of any malignancy or any occurrence of another malignancy that requires active treatment
- The participant completes 35 treatments (approximately 2 years) with pembrolizumab. Note: The number of treatments is calculated starting with the first dose.

For participants who are discontinued from study treatment but continue to be monitored in the trial, see Section 2 – SoA, and Section 9.10.3 – Discontinued Participants Continuing to be Monitored in the Study for those procedures to be completed at each specified visit.

Participants may be allowed to begin study treatment again if deemed medically appropriate.

8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9 – Withdrawal/Discontinuation. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.3.

8.3 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The approximate amount of blood collected from each participant over the duration of the study, including any extra assessments can be found in the procedures manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Administrative and General Procedures

9.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

9.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to Future Biomedical Research. A copy of the informed consent will be given to the participant.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

A medical history will be obtained by the Investigator or qualified designee.

The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the Investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this trial will be recorded separately and not listed as medical history.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this trial will be recorded separately and not listed as a prior medication.

9.1.5.2 Disease Status and Prior Cancer Treatment History

The investigator or qualified designee will also review the participant's current disease status. They will also review all prior anti-cancer treatments including systemic treatments, radiation, and surgeries.

9.1.5.3 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit.

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to treatment allocation. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by non-random assignment and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

Once the participant has achieved the study objective or study has ended, the participant is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

9.1.8 Treatment Administration

Pembrolizumab and the components of the mFOLFOX7 and FOLFIRI chemotherapy regimens will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

When the treatment assignment includes pembrolizumab and one of the chemotherapy regimens (Cohorts B and C and Cohorts D and E) pembrolizumab is to be administered first.

The components of the chemotherapy regimens cannot be given through the same IV line and cannot be given concurrently with pembrolizumab.

Binimetinib (BID dosing): Participants should be instructed to take binimetinib tablets 12 ± 2 hours apart with a large glass of water (~250 mL) in the morning and in the evening at approximately the same times every day. Doses of binimetinib that are omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period.

Standard mFOLFOX7 regimen: oxaliplatin 85 mg/m^2 given concurrently with leucovorin 400 mg/m^2 by IV infusion over 2 hours, 5-FU 2400 mg/m^2 by IV infusion given over 46 to 48 hours.

Standard FOLFIRI regimen: irinotecan 180 mg/m^2 given by IV infusion over 30-90 minutes, leucovorin 400 mg/m^2 given by IV infusion over 2 hours, 5-FU 2400 mg/m^2 by IV infusion over 46 to 48 hours.

9.1.8.1 Timing of Dose Administration

9.1.8.1.1 Pembrolizumab Administration

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab preparation of the infusion fluid and administration.

Every effort should be made to begin the first dose of study treatment on the day of randomization, but if this is not achieved, trial therapy should be initiated no later than 3 days from the date of randomization.

All subsequent cycles of study treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the Investigator's judgment.

All study treatments will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed as detailed on the SoA – Section 2.0.

All study treatments will be administered on an outpatient basis.

9.1.8.1.2 Standard of Care

mFOLFOX7 is a regimen containing oxaliplatin, leucovorin, and 5-FU. Oxaliplatin 85 mg/m^2 is administered over 2 hours on Day 1. Leucovorin 400 mg/m^2 IV is administered over 2 hours on Day 1. 5-FU 2400 mg/m^2 is administered as an IV over 46 to 48 hours IV continuous infusion. mFOLFOX7 is repeated Q2W.

FOLFIRI is a regimen containing irinotecan, leucovorin, and 5-FU. Irinotecan 180 mg/m^2 is administered over 30-90 minutes on Day 1. Leucovorin 400 mg/m^2 IV infusion is administered to match duration of irinotecan infusion on Day 1. 5-FU is administered as 1200 mg/m^2/day for 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion. FOLFIRI is repeated Q2W.

All study treatments will be administered on an outpatient basis.

9.1.8.1.3 Binimetinib

Participants should be instructed to take binimetinib tablets 12 ± 2 hours apart with a large glass of water (~250 mL) in the morning and in the evening at approximately the same times every day.

9.1.9 Withdrawal/Discontinuation

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

9.1.10 Participant Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

9.1.11 Domiciling

Not applicable.

9.1.12 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or

reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

No critical equipment is required. To qualify, sites must have standard equipment and procedures for monitoring vital signs, administering IV medication, and responding to emergencies.

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in SIM. Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1

9.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. Response will be based on RECIST Version 1.1 (Appendix 8) as assessed by investigator/local radiology review. A central imaging vendor will be used to collect, clean, and hold tumor imaging. Images will be collected for possible analysis by blinded, independent central review. The same imaging technique should be used at each time point and the schedule of disease assessment should not be adjusted for delays, if any, in cycle starts of disease assessment.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than

4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the central imaging vendor.

Per iRECIST (Section 9.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 9.2.1.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 9.2.1.5.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks) until the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

9.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, it will be modified for this study. When more than one measurable lesion is present at baseline all lesions up to a maximum of 10 lesions total (and a maximum of 5 lesions per organ) representative of all involved organs should be identified as target if a broader sampling of lesions is needed to provide a more meaningful assessment of overall tumor burden.

9.2.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of

immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has iCPD as defined in Appendix 9, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 9, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 9.

Table 9 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.
Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur.

9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 5.

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 5. Sponsor will closely monitor all AEs, including potential irAEs and overlapping toxicities from drug combination that is tested in this study, and encourage prompt report of any signs and symptoms suggestive of overlapping toxicities, and management of toxicities. Periodic meetings (teleconferences) between the Sponsor and the investigators will be scheduled to discuss the AE findings. On days without a clinic visit during a Cycle (ie, Days 8, 15), AEs should be assessed by telephone.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

Adverse events will not be collected for participants during the pre-screening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy etc., the participant is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.

- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 10.

Table 10 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event		**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period**	**Reporting Time Period: After the Protocol Specified Follow-up Period**		**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required		Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)		Within 24 hours of learning of event
Pregnancy/Lactation Exposure		Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome		Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required		Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required		Within 5 calendar days of learning of event

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 5.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Progression of the cancer under study is not considered a reportable event.

The Sponsor will monitor aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously

reported to the investigator or their designee) that occurs during the trial are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the trial are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 24 hours to the Sponsor if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry

guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

9.3.8 Monitoring Overlapping Toxicities

To ensure the safety of all participants, sponsor will closely monitor all AEs, including irAEs and potential overlapping toxicities from drug combination that is tested in this study, and encourage prompt reporting of any signs and symptoms suggestive of overlapping toxicities, and management of toxicities according to the protocol and local guidelines. Periodic meetings (teleconferences) between the Sponsor and the investigators will be scheduled to discuss the AE findings. Incidence of potential overlapping toxicities in each combination will be closely monitored and compared to that reported in relevant clinical studies. Most importantly, all AEs of unknown etiology associated with drug exposure will be evaluated by investigators to determine if those are possibly immune-related. For suspected irAEs, investigators are required to adequately evaluate and confirm etiology or exclude other causes. Additional procedures or tests may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab alone or discontinue all study treatment, as described in Section 7.2.1.

9.4 Treatment of Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for binimetinib >80 mg BID. For participants treated with pembrolizumab, an overdose will be defined as any dose exceeding ≥1000 mg. For SOC chemotherapy overdose, please refer to the prescribing information and local guidelines. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the drug should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in Section 9.

Planned time points for all safety assessments are provided in the SoA.

9.5.1 Physical Examinations

9.5.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.2 Directed Physical Examination

For cycles that do not required a full physical exam as defined in Section 2, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

9.5.1.3 Full Ophthalmic Examination

Full ophthalmic examination, including best corrected visual acuity for distance testing, automated visual field testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, especially RPED, serous detachment of the retina and RVO, will be performed by an ophthalmologist at screening, Cycle 2 Day 1 and then every 8 weeks from Cycle 2 Day 1 and EOT for participants in Cohorts A, C, and E. An ophthalmic examination at the 30-day follow up is only required if there was a clinically significant abnormality noted at EOT. For all participants, ophthalmic assessments may be performed more frequently per SOC or if clinically indicated for evaluation of any visual signs or symptoms.

9.5.1.4 Additional Testing

Participants with clinical suspicion of retinal abnormalities (ie, RPED, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity), must complete at least one of the following additional assessments:

- For non-vascular abnormalities: OCT of the macula (spectral domain OCT recommended)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.
- Images/results of the ophthalmic examinations (at a minimum, OCT and/or fluorescein angiography) should be sent to the study site and be maintained in the participant's source document file. These images/results may be requested to be sent to the Sponsor or designee.

9.5.2 Vital Signs

Vital signs (temperature, pulse rate, respiratory rate, and blood pressure) will be assessed. The same method of temperature measurement must be used for all participants and must remain the same for each participant. Height will be measured at Visit 1 only.

Blood pressure and pulse measurements should be performed with a completely automated device. Manual techniques will be used only if an automated device is not available. The participant should be in a semi-recumbent or supine position for at least 10 minutes prior to having the measurement performed. The correct size of the blood pressure cuff and correct positioning of the participant's arm are essential to the accuracy of the blood pressure measurement.

9.5.3 Electrocardiograms

- A standard 12-lead ECG will be performed using local standard procedure.

- The ECG measurement performed at the Screening Visit will be used to determine eligibility.
- The ECG measurement at any time point should be used for AE grading and recommended dose modifications.
- When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.

Cohorts A, C, and E

- Triplicate 12-lead ECGs will be obtained at screening only.
    - Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Refer to Section 6.1 (Inclusion Criterion # 12 for QTc withdrawal criteria).
- ECG will be performed predose at every visit starting at Cycle 2 Day 1.

Cohort B and D

- ECG will be performed one time during screening using local standard procedures. Additional time points may be performed as clinically necessary.

9.5.4 Echocardiogram/Multigated Acquisition Scan

Cardiac ejection fraction will be assessed by transthoracic ECHO or MUGA scans at the time points specified in Section 2.0 - SoA. The same method should be used throughout the study. Participants who develop signs/symptoms of CHF at any point during the study are required to have an evaluation of LVEF measurement by ECHO or MUGA.

9.5.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG Performance Status (see Appendix 2) at screening within 7 days prior to the first dose of trial treatment. ECOG Performance Status will be assessed prior to dosing ±3 days of Day 1 of each subsequent treatment cycle, and at discontinuation of trial treatment as specified in the Section 2.0 - Schedule of Activities.

9.5.6 Clinical Safety Laboratory Assessments

Refer to Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Pregnancy test will be performed only on women of child bearing potential. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 24 hours prior to receiving the first dose of study medication. Additional urine/serum pregnancy tests may be performed if clinically warranted, or as defined by local regulations. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

NOTE: Monthly pregnancy testing should be conducted as per local regulations where applicable.

9.5.6.1 Local Laboratory Assessments

All required laboratory tests are specified in Table 11. The schedule of individual laboratory tests is shown in the SoA in Section 2.0.

Table 11 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Specific gravity	Thyroid stimulating hormone (TSH)
Hemoglobin	Alkaline phosphatase	Microscopic exam, if abnormal results are noted	Serum β-human chorionic gonadotropin (β-hCG)[a]
Platelet count	Lactate dehydrogenase (LDH)	Protein	Serum tumor markers (CEA)
White blood cell (WBC) count (total and differential)[b]	Alanine aminotransferase (ALT)	Glucose	Total triiodothyronine (T3) or Free T3 (FT3)[c]
Absolute neutrophil count[d]	Aspartate aminotransferase (AST)	Blood	Free thyroxine (FT4)
Absolute lymphocyte count[d]	Bicarbonate or Carbon dioxide[e]	Protein	PT (INR)
	Calcium	Specific gravity	Activated partial thromboplastin time (aPTT)
	Chloride	Microscopic exam, if abnormal results are noted	Blood for RNA Analyses
	Serum Creatinine		Blood for Plasma Biomarker Analyses

Hematology	Chemistry	Urinalysis	Other
	Creatine phosphokinase (CPK)		Blood for Serum Analyses
	Glucose		Binimetinib pharmacokinetics (PK)
	Potassium		Blood for Genetics Analyses
	Sodium		Blood for Biomarkers
	Total bilirubin		Irinotecan and SN-38 PK
	Direct bilirubin, if total bilirubin is elevated above the ULN		
	Total protein		
	Blood urea nitrogen/Urea[f]		

a. Perform on women of childbearing potential only. Serum pregnancy test is required.
b. Absolute results will be requested for the clinical database.
c. T3 is preferred; if not available free T3 may be tested. If the local laboratory is unable to perform either of these tests the site should submit the sample to the central laboratory for testing; details are provided in the Procedures Manual.
d. Results should be calculated per local standard of practice.
e. If these tests are not done as part of standard of care in your region then these test do not need to be performed.
f. Blood Urea Nitrogen is preferred; if not available urea may be tested.

9.6 Pharmacokinetics

9.6.1 Blood Collection for Binimetinib

Plasma pharmacokinetic studies for binimetinib will be obtained from consenting participants in both Part 1 and Part 2 in Cohort A and E, respectively. Serial plasma samples for PK analysis of binimetinib will be collected at pre-dose, 0.5, 1, 1.5, 2, 4, 6 hours (all ±10 min) on Day 15, pre-dose (24 ± 2 hours from the first binimetinib PK collection) on Day 16 and pre-dose (48 ± 2 hr from the first binimetinib PK collection) on Day 17 in Cycle 1. The exact time of sample collection and time of administration of binimetinib will be recorded. In Cohort E, only one sample is collected at each time point to measure concentrations of binimetinib, irinotecan and active metabolite of irinotecan (SN-38). Sample collection, storage and shipment instructions for plasma samples will be provided in the procedure manual.

9.6.2 Blood Collection for Irinotecan and an Active Metabolite of Irinotecan (SN-38)

Plasma PK studies for irinotecan and an active metabolite of irinotecan (SN-38) will be obtained from consenting participants in both Part 1 and Part 2 in Cohort D and E. Serial plasma samples for PK analysis of irinotecan and an active metabolite of irinotecan (SN-38) will be collected before (pre-infusion), the end of infusion, 1, 1.5, 2, 4, 6 (all ±10 min), 24 ± 2, and 48 ± 2 hours after the initiation of infusion. If irinotecan infusion time is between 45 minutes and 1-hour, then 1-hour sample is not needed, but all other time points apply. The exact time of sample collection (irinotecan and SN-38 will be measured in the same sample) and time of irinotecan administration will be recorded. Sample collection, storage and shipment instructions for plasma samples will be provided in the procedure manual.

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover RNA
- Leftover plasma from biomarker analyses
- Leftover serum from biomarker analyses
- Leftover main study tumor

9.9 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants in this study as specified in the SoA – Section 2. Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

- Blood for Genetic Analysis
- Blood for RNA Analyses
- Blood for plasma biomarker analyses
- Blood for serum biomarker analyses
- Archival or Newly Obtained Tumor Tissue collection
- Post-treatment Tumor Biopsy

9.9.1 Tumor Tissue Collection

Participants will be requested at screening to provide a tumor sample (archival or newly obtained) for biomarker analysis.

The MSI/MMR status must be known prior to enrollment and the participants must be non MSI-H/pMMR. If not known, MSI/MMR status must be performed by the sites' local laboratory using one method ie, IHC or PCR prior to enrollment.

Participants may also agree to provide an optional post-treatment biopsy, for biomarker analysis as outlined in the Schedule of Activities (Section 2). On-study biopsy should be collected on Cycle 2 Day 1 (±3 days).

Sample collection, storage, and shipment instructions for tumor samples will be provided in the Procedures Manual. Archival samples are not required to be submitted within the screening period but must be obtained by the site at the earliest convenient time.

Any leftover samples will be stored for FBR if the participant signs the FBR consent.

9.9.2 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedure Manual. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Approximately 28 of days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 6.1 (Inclusion Criteria) and 6.2 (Exclusion Criteria). Screening procedures may be repeated after consultation with the Sponsor.

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the participant signing consent as part of routine management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment. An exception is hepatitis testing, which may be done up to 28 days prior to the first dose of trial treatment.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of trial treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

9.10.2 Treatment Period

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.3 Discontinued Participants Continuing to be Monitored in the Study

When a participant discontinues study treatment in the treatment or retreatment period, procedures for discontinuation will be performed.

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 2 - Schedule of Activities. Additional details regarding participant withdrawal and discontinuation are presented in Section 8 –Discontinuation/Withdrawal Criteria.

9.10.3.1 Post-Study

Participants will be required to return to clinic approximately 30 days after the last dose of study treatment for the post-trial visit. If the post-trial visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up phone call should be made at 30 days post the last dose of study treatment to determine if any adverse events have occurred since the post-trial clinic visit

9.10.3.2 Safety Follow-up Visits

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

9.10.3.3 Imaging Follow-up Visits

Subjects who discontinue treatment for reasons other than verified PD should continue with imaging assessments per the protocol-defined schedule until: (1) PD is verified or further confirmed by the investigator, (2) initiation of a new anti-cancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first.

9.10.3.4 Follow-up Visits

Participants who discontinue trial treatment for reasons other than disease progression will move into the Follow-up Phase and should be assessed Q9W by radiological imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of a new anti-cancer therapy, disease progression, death, or the end of the study.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

9.10.3.5 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately Q12W until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the efficacy follow-up phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).
- For participants who completed assessments in the efficacy follow-up phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

9.10.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

10. Statistical Analysis Plan

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other non-confirmatory analyses will be outlined in a separate sSAP.

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analyses, will be documented in the sSAP as needed and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

10.1 Statistical Analysis Plan Summary

Trial Design Overview	A Phase 1b Multi-cohort Study of Pembrolizumab (MK-3475) in Combination With Binimetinib and/or Chemotherapy in Participants With Metastatic Colorectal Cancer (KEYNOTE-651)
Analysis Populations	Safety (Primary): All-Participants-as-Treated (APaT) Efficacy (Secondary & Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	Safety: Dose-limiting toxicities (DLTs)
Secondary Endpoints	ORR based on RECIST 1.1 as assessed by the investigator for each cohort.
Statistical Methods for Key Efficacy	The point estimate and 95% CI for ORR will be evaluated separately for each cohort, using exact binomial distribution.

Treatment Assignment	The trial is an open-label trial. Treatment allocation will be accomplished by non-random assignment. If a participant meets the eligibility criteria for Cohorts B and C (ie, previously untreated) or Cohorts D and E (ie, previously treated with one line of fluoropyrimidine-based therapy) then IVRS/IWRS will alternate assignments between the 2 cohorts with the same eligibility criteria. Treatment for each cohort in Part 2 will begin once a preliminary RP2D for that cohort is identified in Part 1.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. The estimates of the DLT rates among participants treated at the RP2D and the 80% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimates will be provided.
Interim Analyses	In this study, data will be examined on a continuous basis to allow for preliminary RP2D decisions (Part 1) and confirmation of RP2D (Part 2). Interim analyses will be conducted at the Sponsor's discretion to enable future trial planning. Futility analyses will be performed in the first 14 evaluable participants treated at the RP2D for each cohort.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The actual sample size depends on the safety profiles and number of doses to be studied. A target sample size of 159 participants will be used for trial planning purposes.

10.2 Responsibility for Analyses/In-House Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The trial is open-label, ie, Participants, Investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.

10.4 Analysis Endpoints

10.4.1 Efficacy Endpoints

Objective response rate is the secondary endpoint of the trial. Objective response rate is defined as the proportion of participants in the analysis population who experience CR or PR using RECIST 1.1 criteria as assessed by investigator review. Other efficacy endpoints (eg, DOR, DCR and PFS based on RECIST 1.1 as assessed by the investigator, ORR, DOR, DCR, and PFS based on iRECIST 1.1 as assessed by the investigator and OS) are exploratory endpoints in this trial and will be defined in the sSAP.

A description of efficacy assessments is provided in Section 9.2.

10.4.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs. Safety and tolerability will be assessed by clinical review throughout the trial. The toxicities and grades experienced by participants who have received study treatment, including AEs, SAEs and ECIs will be summarized. Other safety measures evaluated in study include laboratory tests, ECGs, ECHO/MUGA, vital signs, ECG measurements, physical examinations, and eye examination.

A description of safety measures is provided in Section 9.3.

10.5 Analysis Populations

10.5.1 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study treatment for each cohort. In case of treatment administration errors, participants will be analyzed according to the treatment they actually received. For DLT evaluation, APaT who were observed for safety for 21 days (Cohort A) or 28 days (Cohorts B, C, D, and E) after the first dose of assigned treatment or experienced a DLT prior to 21 days (Cohort A) or 28 days (Cohort B, C, D, and E) after the first dose of assigned treatment will be used.

At least one laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

10.5.2 Efficacy Analysis Population

The FAS population will be used for the analyses of efficacy data in this study. The FAS population consists of all evaluable participants for each cohort with a baseline scan with measurable disease by investigator assessment and received at least 1 dose of study treatment.

10.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

10.6.1 Statistical Methods for Efficacy Analysis

Full Analysis Set population treated at RP2D in each cohort, the point estimate of ORR will be summarized along with a 95% CI using exact binominal method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. Statistical methods for other efficacy analyses will be documented in the sSAP.

10.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, ECIs, laboratory tests, vital signs, ECG measurements, and physical examinations.

Adverse events will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

For Part 1 in each cohort: DLTs will be listed, and further summarized by dose level. The estimates of the DLT rates among participants treated at the RP2D and the 80% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimates will be provided.

10.7 Interim Analyses

In this study, data will be examined on a continuous basis to allow for preliminary RP2D decisions (Part 1) and confirmation of RP2D (Part 2). Interim analyses will be conducted at the Sponsor's discretion to enable future trial planning.

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10.8 Multiplicity

There will be no multiplicity control in this study.

10.9 Sample Size and Power Calculations

For each of the combinations, for Part 1 – dose finding phase: With sample size capped at 14 in each dose level, the maximum sample size in Part 1 is expected to be approximately 28 evaluable participants. In Part 2 – dose confirmation phase, approximately 16 additional participants per cohort will be treated at the RP2D identified in Part 1 to bring the total number of evaluable participants in Part 1 and Part 2 treated at RP2D to approximately 30 for each cohort. The actual sample size depends on the safety profiles and number of doses to be studied. A target sample size of 159 participants will be used for trial planning purposes. The key efficacy endpoint will be ORR based on the investigator assessment per RECIST 1.1. Table 12 shows the ORR estimate and 95% CI (Clopper-Pearson interval) in each cohort.

Table 12 Estimate and 95% Confidence Interval of Objective Response Rate in Each Cohort

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Abbreviations: CI=confidence interval; CR=complete response; ORR=objective response rate; PR=partial response.

10.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP.

10.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the trial. Any deviation from protocol-directed administration will be reported.

10.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation	Definition
1L	first line
2L	second line
5-FU	fluorouracil
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
APaT	All-Participants-as-Treated
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	Adenosine triphosphate
BCRP	breast cancer resistance protein
β-hCG	human chorionic gonadotropin
BICR	Blinded Independent Central Review
BID	twice daily
CEA	carcinoembryonic antigen
CD3ζ	CD3 zeta
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	Clinical Study Report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocytes
CTL-4	cytotoxic T lymphocytes-associated protein 4
CVA	cerebrovascular accidents
DCR	disease control rate
DILI	drug-induced liver injury
DBP	diastolic blood pressure
DL	dose level
DL1	Standard dose
DL-1	de-escalation dose
DL2	escalation dose
DLT	dose-limiting toxicity

Abbreviation	Definition
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram
EDC	electronic data capture
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EOT	end of trial
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FOLFIRI	(irinotecan [180 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2)
FOLFOX, mFOLFOX6, mFOLFOX7	(oxaliplatin [85 mg/m^2]; leucovorin [calcium folinate] [400 mg/m^2]; 5-FU 2400 mg/m^2)
5-FU	fluorouracil
GCP	Good Clinical Practice
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNSCC	head and neck squamous cell carcinoma
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
IgG4	immunoglobulin G4
IHC	immunohistochemistry
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB/IEC	Institutional Review Board/Independent Ethics Committee
iRECIST	modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
iSD	iRECIST stable disease
iUPD	iRECIST unconfirmed progressive disease

Abbreviation	Definition
IV	intravenous
IVRS/IWRS	interactive voice response system, integrated web response system
LVEF	left ventricular ejection fraction;
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care
mCRC	metastatic colorectal cancer
MHC1	major histocompatibility complex1
MMR	mismatch repair
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	microsatellite instability high
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PABA	para-aminobenzoic acid
PBPK	physiologically-based pharmacokinetic
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PKCθ	protein kinase C-theta
pMMR	proficient mismatch repair
PO	oral
PSN	peripheral sensory neuropathy
PSVT	paroxysmal supraventricular tachycardia
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
Q2W	every 2 weeks
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks

Abbreviation	Definition
QTc	Q-T interval
QTcF	QT interval calculated according to the Fridericia method
RECIST 1.1	Response Evaluation Criteria In Solid Tumors 1.1
RP2D	recommended Phase 2 dose
RPED	retinal pigment epithelial detachment
RNA	ribonucleic acid
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SIM	Site Imaging Manual
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental statistical analysis plan
T3, T4	triiodothronine, thyroxine
TCR	T-cell receptor
TIA	transient ischemic attacks
TIL	tumor infiltrating lymphocyte
TMDD	target-mediated drug disposition
TPS	tumor proportion score
T-reg	Regulatory T cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UVA	ultraviolet A
UVB	ultraviolet B
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WOCBP	woman of childbearing potential
ZAP70	zeta-chain-associated protein kinase

12.2 Appendix 2: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.3 Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 6.1 and 6.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH		WBC count (total and differential)[a]: Absolute neutrophil count[b] Absolute lymphocyte count[b] Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN)[c]	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate or Carbon dioxide[d]	Chloride	LDH
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
	Creatine phosphokinase (CPK)			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Thyroid stimulating hormone (TSH) • Serum tumor markers (CEA [carcinoembryonic antigen]) • Total triiodothyronine (T3) or Free T3 (FT3)[e] • Free thyroxine (FT4) • PT (INR) • aPTT • Serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test (as needed for women of childbearing potential)[f] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] [if applicable] • All study-required laboratory assessments will be performed by a local laboratory, with the exception of: Blood for ribonucleic acid (RNA) analyses, blood for plasma biomarker analyses, binimetinib pharmacokinetics (PK), Blood for genetics analyses, and irinotecan and SN-38 PK			

Laboratory Assessments	Parameters

NOTES:

a. Absolute results will be requested for the clinical database.
b. Results should be calculated per local standard of practice.
c. Blood Urea Nitrogen is preferred; if not available urea may be tested.
d. If these tests are not done as part of standard of care in your region then these test do not need to be performed.
e. T3 is preferred; if not available free T3 may be tested. If the local laboratory is unable to perform either of these tests the site should submit the sample to the central laboratory for testing; details are provided in the Procedures Manual.
f. Perform on women of childbearing potential only. Serum pregnancy test is required.

Investigators must document their review of each laboratory safety report.

12.4 Appendix 4: Study Governance Considerations

Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

Publication Policy

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated

Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from

source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.5 Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
● An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. ● NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. ● NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study.

Events <u>Meeting</u> the AE Definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. ● Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. ● New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. ● Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. ● Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. ● For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." ● Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

Events NOT Meeting the AE Definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to section 9.3.5 for protocol specific exceptions

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a MSD product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse event to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool
● The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool. ● Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent). ● If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form. ● Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements ● The site will enter the SAE data into the electronic system as soon as it becomes available. ● After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. ● If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section). ● Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).
SAE Reporting to the Sponsor via Paper CRF
● If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor. ● In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. ● Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. ● Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

12.6 Appendix 6: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 6.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 14 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 14 consistently and correctly during the protocol-defined time frame in Section 6.1.

Table 14 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception[b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

12.7 Appendix 7: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in Future Biomedical Research.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the participants on the visit designated in the trial flow chart. If delayed, present consent at next possible Participant Visit. Consent forms

signed by the participant will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the participant is having blood drawn for other trial purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in Future Biomedical Research and consent. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If

medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to

rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (ie, only leftover samples are being retained).]

The Sponsor has developed strict security, policies and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.8 Appendix 8: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response.

While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study. Details are provided in the Image Acquisition Guidelines.

* As published in the European Journal of Cancer:

New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer. 2009 Jan;45(2):228-247.

12.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1, the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management) (see Table 9). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD and iCPD. For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment. *Detection of Progression at Visits after Pseudo-progression Resolves*

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].